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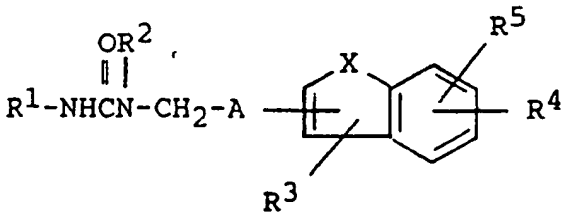
(54) Title: N'-HETEROCYCLYL-N-BENZOFURANYL UREA DERIVATIVES AND THEIR ANALOGS AS ACAT INHIBITORS

(57) Abstract

This invention relates to new urea derivatives having an inhibitory activity against acyl-CoA:cholesterol acyltransferase enzyme and represented by general formula (I), wherein R^1 is a heterocyclic group which may be substituted with lower alkyl, etc., R^2 is lower alkyl, etc., R^3 is hydrogen, lower alkyl or aryl which may be substituted with halogen, etc., R^4 is hydrogen, halogen, lower alkyl, lower alkoxy or acyl which may be substituted with halogen, R^5 is aryl, etc., A is a single bond, etc., and X is O, etc., provided that at least one of unsubstituted or substituted aryl for R^3, R^4 and R^5 is aryl except phenyl or substituted aryl, and pharmaceutically acceptable salts thereof, to processes for the preparation thereof and to a pharmaceutical composition comprising the same.



(I)

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DESCRIPTION

N'-HETEROCYCLYL-N-BENZOFURANYL UREA DERIVATIVES AND THEIR ANALOGS AS ACAT INHIBITORS

TECHNICAL FIELD

This invention relates to new urea derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some urea derivatives have been known as acyl-CoA : cholesterol acyltransferase enzyme (hereinafter, ACAT) inhibitors, for example, in U.S.Patent Nos. 4,473,579 and 4,623,662, EP Patent Application Publication Nos. 0354994, 0399422 and 0512570 and PCT International Publication Nos. WO 91/13871 and WO 93/24458.

DISCLOSURE OF INVENTION

This invention relates to new urea derivatives and pharmaceutically acceptable salts thereof.

More particularly, it relates to new urea derivatives and pharmaceutically acceptable salts thereof which have an inhibitory activity against ACAT and an advantage of good absorption into blood on oral administration, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

One object of this invention is to provide new and useful urea derivatives and pharmaceutically acceptable salts which possess an inhibitory activity against ACAT.

Another object of this invention is to provide processes for preparation of said urea derivatives and salts thereof.

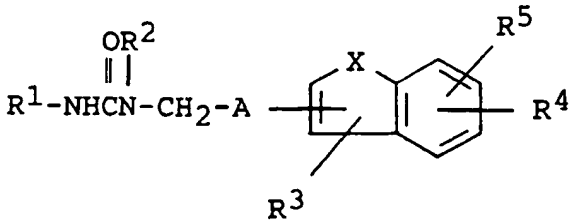
A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said urea derivatives and pharmaceutically acceptable salts thereof.

Still further object of this invention is to provide a therapeutic method for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby in human beings or animals, using said urea derivatives and pharmaceutically acceptable salts thereof.

High levels of blood cholesterol and blood lipids are conditions which are involved in the onset of atherosclerosis.

It is well known that inhibition of ACAT-catalyzed cholesterol esterification could lead to diminish intestinal absorption of cholesterol as well as a decrease in the intracellular accumulation of cholesterol esters in the intima of the arterial wall. Therefore, ACAT inhibitors are useful for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis of diseases caused thereby such as cardiac insufficiency (e.g. angina pectoris, myocardial infarction, etc.), cerebrovascular disturbance (e.g. cerebral infarction, cerebral apoplexy, etc.), arterial aneurism, peripheral vascular disease, xanthomas, restenosis after percutaneous transluminal coronary angioplasty, or the like.

The object urea derivatives of this invention are new and can be represented by the following general formula (I) :



(I)

wherein R^1 is a heterocyclic group which may be substituted with substituent(s) selected from the group consisting of lower alkyl, lower alkylthio, halogen, nitro, amino, lower alkylamino, lower alkoxy and acylamino,

R^2 is hydrogen; alkyl; lower alkenyl; cycloalkyl; or lower alkyl which is substituted with halogen, lower alkoxy, lower alkylthio, cyclo(lower)alkyl, cyclo(lower)alkenyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy, lower alkoxy, ar(lower)alkoxy and lower alkylamino;

R^3 is hydrogen, lower alkyl or aryl which may be substituted with halogen, nitro, amino or lower alkylamino,

R^4 is hydrogen, halogen, lower alkyl, lower alkoxy or aryl which may be substituted with halogen,

R^5 is hydrogen, halogen, lower alkyl or aryl,

A is a single bond or lower alkylene, and

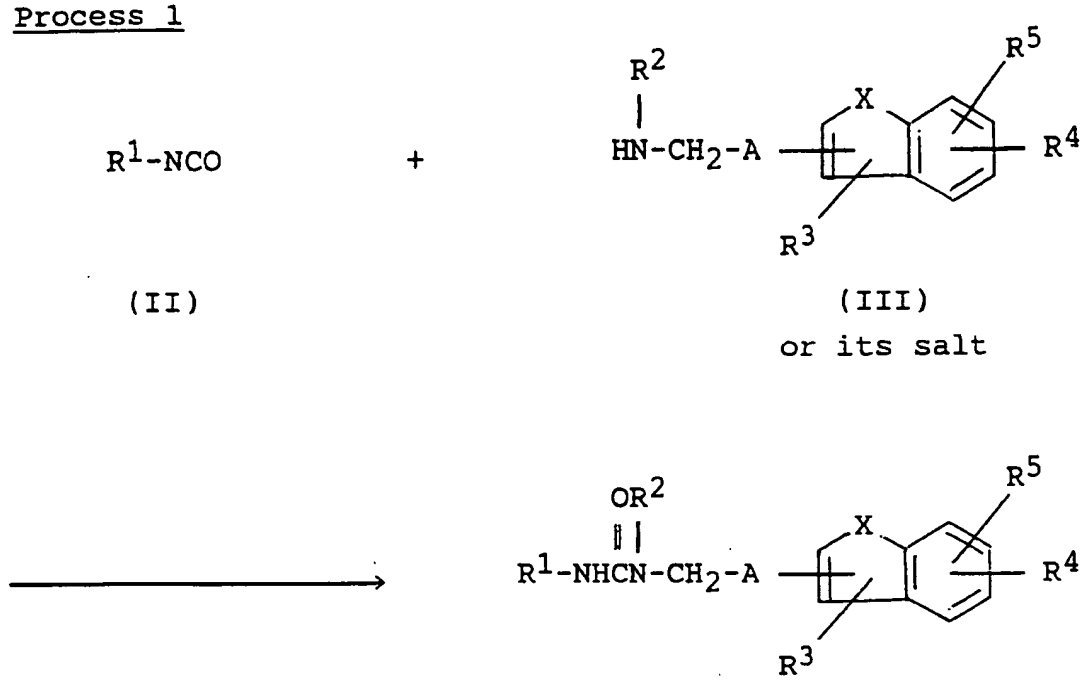
X is O, S or NH,

provided that at least one of unsubstituted or substituted aryl for R^3, R^4 and R^5 is aryl except phenyl or substituted aryl,

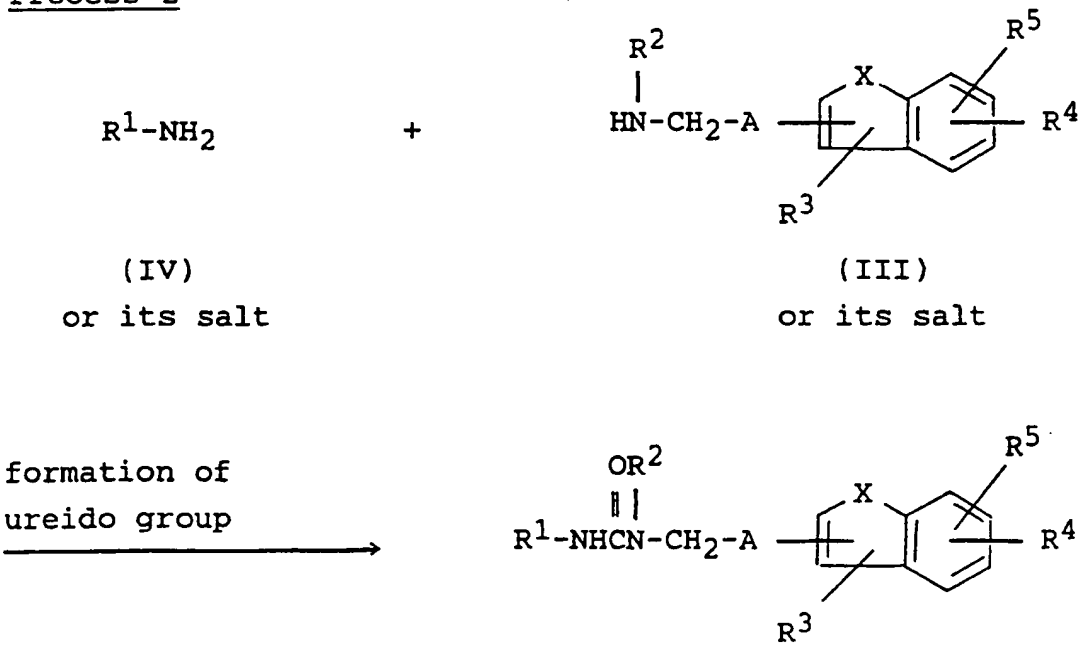
and pharmaceutically acceptable salts thereof.

The object compound (I) or its salt can be prepared by processes as illustrated in the following reaction schemes.

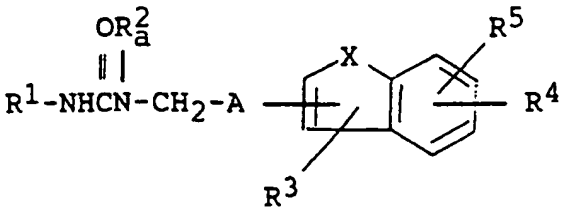
Process 1



Process 2

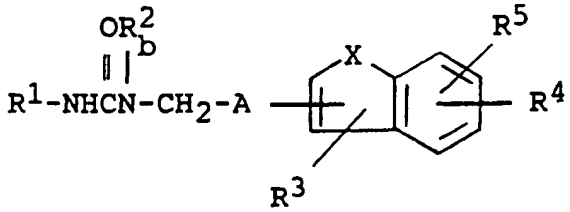


Process 3



dealkylation

(Ia)
or its salt



(Ib)
or its salt

wherein R^1, R^2, R^3, R^4, R^5, A and X are each as defined above,

R^2_a is lower alkyl which is substituted with aryl substituted with lower alkoxy, and

R^2_b is lower alkyl which is substituted with aryl substituted with hydroxy.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The lower moiety in the terms "lower alkenyl" and "lower alkenylene" are intended to mean a group having 2 to 6 carbon atoms.

The lower moiety in the term "cyclo(lower)alkyl" is

intended to mean a group having 3 to 6 carbon atoms.

The lower moiety in the term "cyclo(lower)alkenyl" is intended to mean a group having 3 to 6 carbon atoms.

The term "alkyl" may include lower alkyl and higher alkyl.

The term "cycloalkyl" may include cyclo(lower)alkyl and cyclo(higher)alkyl.

Suitable "lower alkyl" and lower alkyl moiety in the terms "lower alkylthio", "lower alkylamino" and "ar(lower)alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl or the like, in which preferable one is one having 1 to 5 carbon atom(s) such as methyl, ethyl, propyl, isopropyl, isobutyl, pentyl or isopentyl.

Preferable one in alkyl for R^2 is alkyl having 3 to 7 carbon atoms, in which more preferable one is isopentyl.

Suitable "cyclo(lower)alkyl" may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Suitable "lower alkenyl" may be a straight or branched one such as ethenyl, propenyl, pentenyl (e.g. 2-pentenyl, 3-pentenyl or 4-pentenyl), isopropenyl, butenyl (e.g. 2-butenyl or 3-butenyl), hexenyl or the like, in which preferable one is butenyl.

Suitable "cyclo(lower)alkenyl" may be cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

The term "higher" is intended to mean 7 to 20 carbon atoms, unless otherwise provided.

Suitable "higher alkyl" may be a straight or branched one such as heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, methylheptyl, methyloctyl, methylnonyl, methyldecyl, ethylheptyl, ethyloctyl, ethylnonyl, ethyldecyl or the like, in which preferable one is one having 7 to 10 carbon atoms and the most

preferable one is heptyl or nonyl.

Suitable "cyclo(higher)alkyl" may be cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclotridecyl, cyclotetradecyl, cyclopentadecyl, cyclohexadecyl, cycloheptadecyl, cyclooctadecyl, cyclononadecyl, cycloeicosyl, in which preferable one is one having 7 to 10 carbon atoms and the most preferable one is cycloheptyl.

Suitable "lower alkoxy" and lower alkoxy moiety in the term "ar(lower)alkoxy" may be a straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which preferable one is methoxy.

Suitable "halogen" may be fluorine, chlorine, bromine and iodine, in which preferable one is fluorine, chlorine or bromine.

Suitable "lower alkylthio" may be a straight or branched one such as methylthio, ethylthio, propylthio, isopropylthio, pentylthio or the like, in which preferable one is methylthio.

Preferable one in lower alkyl substituted with halogen for R^2 is lower alkyl substituted with fluorine, in which more preferable one is heptafluorobutyl.

Preferable one in lower alkyl substituted with lower alkoxy for R^2 is lower alkyl substituted with methoxy, in which more preferable one is methoxyethyl.

Preferable one in lower alkyl substituted with lower alkylthio for R^2 is lower alkyl substituted with methylthio, in which more preferable one is methylthioethyl.

Preferable one in lower alkyl substituted with cyclo(lower)alkyl for R^2 is lower alkyl substituted with cyclopropyl, in which more prefeable one is cyclopropylmethyl.

"N-Protective group" may be common N-protective group

such as acyl, for example, substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], phthaloyl, lower alkoxycarbonyl [e.g. tert-butoxycarbonyl, tert-amyloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, ar(lower)alkyl [e.g. trityl, benzyl, etc.] or the like, in which preferable one is unsubstituted lower alkanoyl such as trifluoroacetyl.

Suitable "esterified carboxy" may be substituted or unsubstituted lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsustituted ar(lower)alkoxycarbonyl [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.] and the like, in which preferable one is lower alkoxycarbonyl.

Suitable "aryl" and ar moiety in the term "ar(lower)alkoxy" may be phenyl, naphthyl, phenyl substituted with lower alkyl (e.g. tolyl, xylyl, mesityl, cumenyl, diisopropylphenyl, etc.) and the like, in which preferable one is phenyl or phenyl substituted with lower alkyl.

Suitable "lower alkylamino" may be mono or di(lower alkyl)amino such as methylamino, ethylamino, dimethylamino, diethylamino or the like, in which preferable one is dimethylamino.

Suitable "ar(lower)alkyl" may be phenyl(lower)alkyl (e.g. benzyl, phenethyl, phenylpropyl, etc.), benzhydryl, trityl, tolylmethyl, xylylmethyl, mesitylmethyl,

cumenylmethyl, and the like, in which preferable one is phenyl(lower)alkyl and the most preferable one is benzyl.

Suitable "lower alkylene" may be a straight or branched one such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene, ethylethylene, or the like.

The aryl groups for R^3 and R^4 may be substituted with 1 to 5 substituent(s) as mentioned above, wherein the preferable number of the substituent(s) is 1, 2 or 3.

The aryl group as substituent of lower alkyl for R^2 may be substituted with 1 to 5 substituent(s) as stated above, wherein the preferable number of the substituent(s) is 1, 2 or 3.

Preferable "aryl substituted with halogen" is chlorophenyl, dichlorophenyl, difluorophenyl, trichlorophenyl or trifluorophenyl.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom.

The preferred examples of thus defined "heterocyclic group" may be unsaturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, tetrahydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl, tetrazolyl, etc.;

saturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl,

indazolyl, benzotriazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl, etc.;

saturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino, sydnonyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example thiazolyl, isothiazolyl, thiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example, benzofuranyl, etc.; or the like.

Preferable one in a heterocyclic group for R^1 is pyridyl or quinolyl.

Preferable one in lower alkyl substituted with a heterocyclic group for R^2 is lower alkyl substituted with furyl or thienyl, in which more preferable one is furylmethyl or thienylmethyl.

Suitable acyl moiety in the term "acylamino" may be

carboxy; esterified carboxy; carbamoyl optionally substituted with substituent(s) selected from the group consisting of lower alkyl, cyclo(lower)alkyl, aryl and hydroxy; lower alkanoyl; a heterocycliccarbonyl; lower alkylsulfonyl; and the like.

The esterified carboxy may be substituted or unsubstituted lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyl [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.] and the like.

The lower alkanoyl may be formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and the like, in which preferable one is acetyl.

The heterocyclic moiety in the term "heterocycliccarbonyl" may be the same as those exemplified for "heterocyclic group".

The lower alkylsulfonyl may be methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like, in which the preferable one is methylsulfonyl.

Suitable "acylamino" may be lower alkanoylamino and lower alkylsulfonylamino, in which preferable one is acetylamino or methylsulfonylamino.

The heterocyclic group for R^1 may be substituted with singular or plural substituent(s) as mentioned above, wherein the preferable number of the substituent(s) is 1 to 3.

Preferable compound (I) is one which has a heterocyclic group (more preferably pyridyl or quinolyl) optionally substituted with substituent(s) selected from

the group consisting of lower alkyl and lower alkylthio for R^1, alkyl, cycloalkyl, or lower alkyl substituted with cyclo(lower)alkyl, a heterocyclic group (more preferably furyl or thienyl), aryl (more preferably phenyl or phenyl substituted with lower alkyl) optionally substituted with halogen, hydroxy, lower alkoxy, ar(lower)alkoxy or lower alkylamino for R^2, aryl except phenyl (more preferably phenyl substituted with lower alkyl) or aryl (more preferably phenyl or phenyl substituted with lower alkyl) substituted with halogen for R^3, lower alkyl or halogen for R^4, hydrogen for R^5, a single bond for A, and O for X.

More preferable compound (I) is one which has a heterocyclic group (more preferably pyridyl or quinolyl) optionally substituted with substituent(s) selected from the group consisting of lower alkyl and lower alkylthio for R^1, alkyl, or lower alkyl substituted with furyl or aryl (more preferably phenyl or phenyl substituted with lower alkyl) for R^2, aryl except phenyl (more preferably phenyl substituted with lower alkyl) or aryl (more preferably phenyl or phenyl substituted with lower alkyl) substituted with halogen for R^3, lower alkyl for R^4, hydrogen for R^5, a single bond for A, and O for X.

Most preferable compound (I) is one which has pyridyl or quinolyl, each of which is substituted with substituent(s) selected from the group consisting of lower alkyl and lower alkylthio for R^1, alkyl having 3 to 7 carbon atoms, or lower alkyl substituted with furyl or phenyl for R^2, phenyl substituted with lower alkyl or halogen for R^3, lower alkyl for R^4, hydrogen for R^5, a single bond for A, and O for X.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate,

maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an alkali metal salt [e.g. sodium salt, potassium salt, etc.] or the like.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) or its salt can be prepared by reacting a compound (II) with a compound (III) or its salt.

Suitable salt of the compound (III) may include an acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic base salt [e.g. sodium salt, potassium salt, etc.] or the like.

The reaction is usually carried out in a conventional solvent such as dioxane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, or any other organic solvent which does not adversely influence the reaction.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is preferably carried out under cooling or at ambient temperature.

Process 2

The object compound (I) or its salt can be prepared by subjecting a compound (IV) or its salt and a compound (III) or its salt to formation reaction of ureido group.

Suitable salts of the compounds (III) and (IV) may be the same as those exemplified for the compound (I).

This reaction is carried out in the presence of reagent which introduces carbonyl group such as phosgene, haloformate compound [e.g. ethyl chloroformate, trichloromethyl chloroformate, phenyl chloroformate, etc.], N,N'-carbonyldiimidazole, metal carbonyl compounds [e.g. cobalt carbonyl, manganese carbonyl, etc.], a combination of carbon monoxide and catalysts such as palladium chloride, etc., or the like.

This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, toluene, chloroform, methylene chloride, N,N-dimethylformamide, ethyl acetate or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

In this reaction, in case that a compound (IV) or its salt is firstly reacted with a reagent introducing carbonyl group and the product obtained thereby is stable, that product may be isolated and then reacted with a compound (III) or its salt to obtain a compound (I) or its salt. This case is included within the scope of the present reaction. In such case, the reaction is preferably carried out in the presence of a base such as N,N-dimethylaniline, triethylamine or the like.

Process 3

The object compound (Ib) or its salt can be prepared by subjecting a compound (Ia) or its salt to dealkylation reaction.

Suitable salts of the compounds (Ia) and (Ib) may be acid addition salts as exemplified for the compound (I).

The reaction is carried out in the presence of an acid including Lewis acid [e.g. hydrochloric acid,

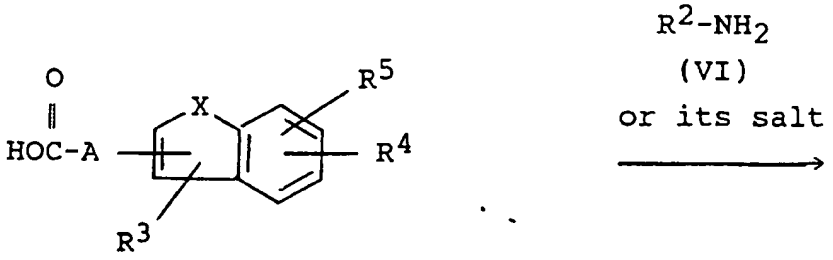
hydrobromic acid, hydroiodic acid, boron tribromide, boron trichloride, etc.] or tri(lower alkyl)silyliodide [e.g. trimethylsilyliodide, etc.].

The reaction is usually carried out in a solvent such as water, acetic acid, methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction.

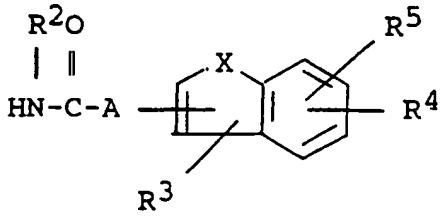
The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Among the starting compound (III), some of them are new and can be prepared by processes as illustrated in the following reaction schemes.

Process A

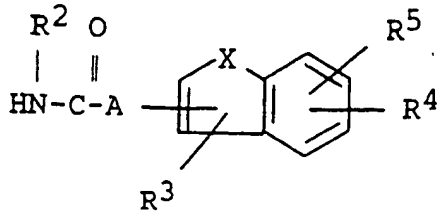


(V)
or its reactive derivative
at the carboxy group
or a salt thereof



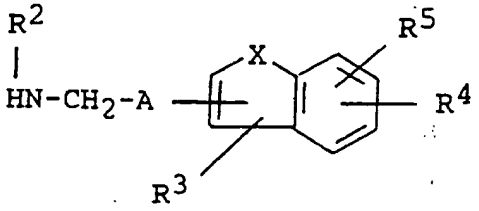
(VII)
or its salt

Process B



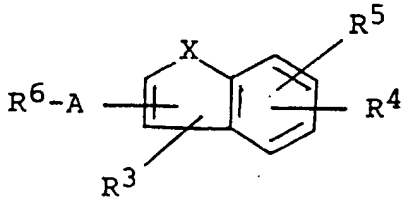
reduction

(VII)
or its salt



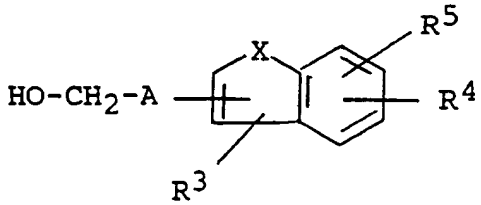
(III)
or its salt

Process C



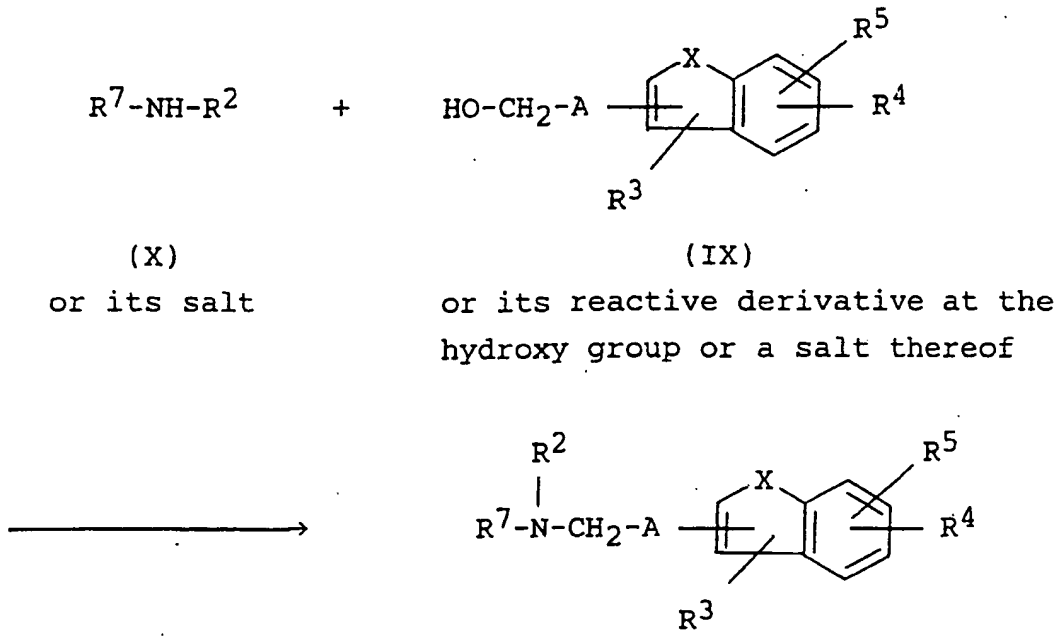
reduction

(VIII)
or its salt



(IX)
or its salt

Process D

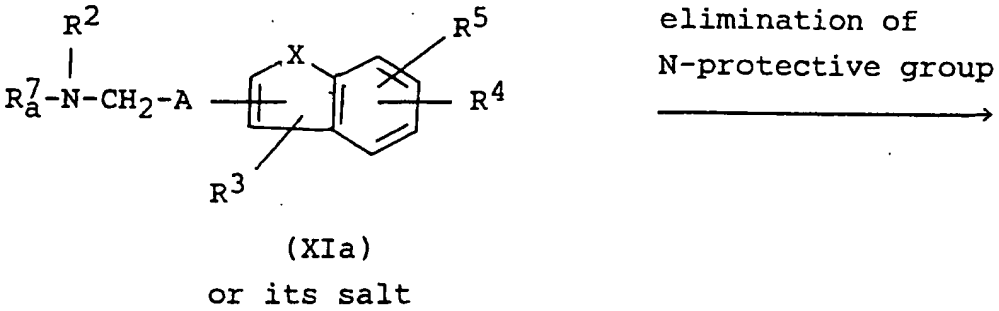


(X)
or its salt

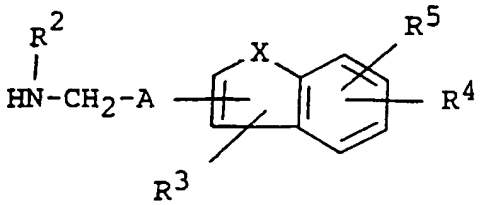
(IX)
or its reactive derivative at the hydroxy group or a salt thereof

(XI)
or its salt

Process E



(XIa)
or its salt



(III)
or its salt

wherein R^2, R^3, R^4, R^5, A and X are each as defined above,
R^6 is carboxy or esterified carboxy,
R^7 is hydrogen or N-protective group, and
R^7_a is N-protective group.

The above-mentioned processes for preparing the starting compound are explained in detail in the following.

Process A

The compound (VII) or its salt can be prepared by reacting a compound (V) or its reactive derivative at the carboxy group or a salt thereof with a compound (VI) or its salt.

Suitable salts of the compounds (V), its reactive derivative and the compounds (VI) and (VII) may be the same as those exemplified for the compound (I).

Suitable reactive derivative of the compound (V) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. The suitable example amy be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid (e.g. methanesulfonic acid, etc.), alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester,

dimethyliminomethyl [$(CH_3)_2N^+$=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with an N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, 1-hydroxy-6-chloro-1H-benzotriazole, etc.) and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (V) to be used.

The reaction is usually carried out in a conventional solvent such as water, an alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

When the compound (V) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus

trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylforamamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical and the reaction can be carried out under cooling to heating.

Process B

The compound (III) or its salt can be prepared by reacting a compound (VII) or its salt with a reducing agent.

Suitable salt of the compound (VII) may be the same as those exemplified for the compound (I).

Suitable reducing agent may be diborane, metal hydride [e.g. lithium aluminum hydride, etc.], a combination of metal hydride [e.g. lithium aluminum hydride, etc.] and Lewis acid [e.g. aluminum chloride, etc.], and the like.

The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process C

The compound (IX) or its salt can be prepared by

reacting a compound (VIII) or its salt with a reducing agent.

Suitable salts of the compounds (VIII) and (IX) may be the same as those exemplified for the compound (I).

Suitable reducing agent may be aluminum hydride compound [e.g. lithium aluminum hydride, lithium tri-t-butoxyaluminum hydride, etc.], borohydride compound [e.g. sodium borohydride, etc.], aluminum alkoxide [e.g. aluminum isopropoxide, etc.] and the like.

The reaction is usually carried out in a conventional solvent, such as water, an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], chloroform, diethyl ether tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process D

The compound (XI) or its salt can be prepared by reacting a compound (X) or its salt with a compound (IX) or its reactive derivative at the hydroxy group or a salt thereof.

Suitable salt of the compound (X) may be an acid addition salt as exemplified for the compound (I).

Suitable salts of the compound (IX) and its reactive derivative at the hydroxy group may be the same as those exemplified for the compound (I).

Suitable reactive derivative at the hydroxy group of the compound (IX) may be one having acid residue such as halogen (e.g. fluoro, chloro, bromo, iodo), arenesulfonyloxy (e.g. benzenesulfonyloxy, tosyloxy, etc.), alkanesulfonyloxy (e.g. mesyloxy, ethanesulfonyloxy, etc.), and the like, in which preferable derivative is one having halogen.

The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran, dioxane, methylene chloride, N,N-dimethylformamide, 1,3-dimethyl-2-imidazolidinone or any other organic solvent which does not adversely influence the reaction.

When the reactive derivative at the hydroxy group of the compound (IX) is one having halogen, the reaction is preferably carried out in the presence of a base such as alkali metal [e.g. lithium, sodium, potassium, etc.], the hydroxide or carbonate or bicarbonate thereof [e.g. sodium hydroxide, potassium carbonate, potassium bicarbonate, etc.], alkaline earth metal [e.g. calcium, magnesium, etc.], alkali metal hydride [e.g. sodium hydride, etc.], alkaline earth metal hydride [e.g. calcium hydride, etc.], alkali metal alkoxide [e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.], alkaline earth metal alkoxide [e.g. magnesium methoxide, magnesium ethoxide, etc.] or the like, alkali metal iodide [e.g. sodium iodide, potassium iodide, etc.] or a mixture thereof.

When the compound (IX) is used in a hydroxy form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dichlorohexylcarbodiimide;
N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide;
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;
N,N'-carbonylbis-(2-methylimidazole);
pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine; ethoxyacetylene;
1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride;
diphenyl phosphorylazide; diphenyl chlorophosphate;

diphenylphosphinic chloirde; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling o heating.

Process E

The compound (III) or its salt can be prepared by subjecting a compound (XIa] or its salt to elimination reaction of the N-protective group.

Suitable salts of the compounds (III) and (XIa) may be the same as those exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the lie.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g.

hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, etc.] and an acid addition salt compound [e.g. pyridine hydrochloride, etc.].

The elimination using trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, tetrachloromethane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g.

reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

In case that the N-protective group is benzyl, the reduction is preferably carried out in the presence of a combination of palladium catalysts [e.g. palladium black, palladium on carbon, etc.] and formic acid or its salt [e.g. ammonium formate, etc.].

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g. methanol, ethanol, propanol, etc.], chlorobenzene, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixture thereof are included within the scope of this invention.

The object compounds (I) and pharmaceutically acceptable salts thereof possess a strong inhibitory

activity against ACAT, and are useful for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compounds of the compound (I) are shown in the following.

Test :

Acyl-CoA : cholesterol acyltransferase (ACAT) inhibitory activity

Method :

ACAT activity was measured by the method of Heider et al. described in Journal of Lipid Research, Vol. 24, page 1127 (1983). The enzyme ACAT was prepared from the mucosal microsome fraction of the small intestine of male, 18-week old Japanese white rabbits which had been fed diet containing 2% cholesterol for 8 weeks. The inhibitory activity of compounds were calculated by measuring the amount of the labeled cholesterol ester produced from [^{14}C]oleoyl-CoA and endogenous cholesterol as follows. [^{14}C]Oleoyl-CoA and microsome were incubated with test compounds at 37°C for 5 minutes. The reaction was stopped by the addition of chloroform-methanol (2:1, V/V). Cholesterol ester fraction in the chloroform-methanol extracts was isolated by thin-layer chromatography and was counted their label.

Result :

Test Compound (Example No.)	IC_{50} (M)
1	3.4×10^{-8}
2-24)	2.5×10^{-8}
5	2.3×10^{-8}

For therapeutic purpose, the compound (I) of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external (topical) administration, wherein more preferable one is oral administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

To a stirred solution of 3-(4-chlorophenyl)-5-methylbenzofuran-2-carboxylic acid (2 g) and N,N-dimethylformamide (1 drop) in methylene chloride (20 ml) was added oxalyl chloride (1 ml) at ambient temperature and the mixture was stirred at the same temperature for 2 hours. Evaporation of solvent and excess oxalyl chloride gave crude 3-(4-chlorophenyl)-5-methylbenzofuran-2-carbonyl chloride (2.1 g). To a stirred solution of 4-benzyloxybenzylamine (1.6 g) and triethylamine (1.6 ml) in methylene chloride (10 ml) was added dropwise a solution of the acid chloride (2.1 g) at 0°C and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was washed with diluted hydrochloric acid and aqueous 5% sodium bicarbonate, and dried. Evaporation of solvent gave a residue which was recrystallized from ethyl acetate (2 ml) - n-hexane (6 ml) gave N-(4-benzyloxybenzyl)-3-(4-chlorophenyl)-5-methylbenzofuran-2-carboxamide (3.1 g).

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.53 (2H, d, J=6Hz), 5.07 (2H, s), 6.86 (1H, t, J=6Hz), 6.97 (2H, d, J=9Hz), 7.25-7.48 (12H, m), 7.62 (2H, d, J=9Hz)

Preparation 2

The following compounds were obtained according to a similar manner to that of Preparation 1.

1) N-(2-Fluorobenzyl)-5-methyl-3-(4-methylphenyl)-benzofuran-2-carboxamide

NMR ($CDCl_3$, δ) : 2.43 (6H, s), 4.66 (2H, d, J=5Hz), 6.87 (1H, br t, J=5Hz), 7.00-7.15 (2H, m), 7.22-7.56 (9H, m)

2) N-Heptyl-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.28 (10H, br s), 2.42 (6H, s), 3.40 (2H, q, J=7Hz), 6.48 (1H, t, J=7Hz), 7.24-7.56 (7H, m)

3) N-Cyclobutyl-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 1.67-2.00 (6H, m), 2.42 (6H, s), 4.55 (1H, sext, J=7.5Hz), 6.65 (1H, d, J=7.5Hz), 7.22-7.57 (7H, m)

4) N-(4-Methylbenzyl)-5-methyl-3-(4-methylphenyl)-benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.36 (3H, s), 2.43 (6H, s), 4.56 (2H, d, J=5Hz), 6.77 (1H, br t, J=5Hz), 7.12-7.40 (9H, m), 7.55 (2H, d, J=9Hz)

5) N-(4-Chlorobenzyl)-5-methyl-3-(4-methylphenyl)-benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.42 (6H, s), 4.58 (2H, d, J=5Hz), 6.82 (1H, br t, J=5Hz), 7.22-7.43 (9H, m), 7.53 (2H, d, J=9Hz)

6) 3-(4-Chlorophenyl)-5-methyl-N-(4-dimethylamino-benzyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 2.96 (6H, s), 4.50 (2H, d, J=5.5Hz), 6.70-6.85 (3H, m), 7.21-7.39 (5H, m), 7.54 (4H, AB, J=9.5, 9Hz)

7) 3-(4-Chlorophenyl)-5-methyl-N-(2-methylpropyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.97 (6H, d, J=7.5Hz), 1.89 (1H, septet, J=7.5Hz), 2.45 (3H, s), 3.27 (2H, t, J=7.5Hz), 6.69 (1H, br t, J=7.5Hz), 7.29-7.46

(3H, m), 7.54 (4H, AB, J=8, 7.5Hz)

8) 5-Methyl-3-(4-methylphenyl)-N-(2-methylpropyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.91 (6H, d, J=7Hz), 1.84 (1H, septet, J=7Hz), 2.44 (6H, s), 3.23 (2H, t, J=7Hz), 6.52 (1H, br t, J=7Hz), 7.24-7.53 (7H, m)

9) 5-Methyl-3-(4-methylphenyl)-N-(2-thienylmethyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.44 (3H, s), 4.78 (2H, d, J=7Hz), 6.82 (1H, br t, J=7Hz), 6.95-7.02 (2H, m), 7.24-7.42 (6H, m), 7.53 (2H, d, J=8Hz)

10) N-(3-Chlorobenzyl)-3-(4-chlorophenyl)-5-methylbenzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.49 (3H, s), 4.62 (2H, d, J=7Hz), 6.98 (1H, br t, J=7Hz), 7.29-7.67 (11H, m)

11) N-(3-Chlorobenzyl)-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.41 (6H, s), 4.58 (2H, d, J=7Hz), 6.81 (1H, br t, J=7Hz), 7.18-7.54 (11H, m)

12) N-(3-Fluorobenzyl)-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.44 (6H, s), 4.60 (2H, d, J=6Hz), 6.82 (1H, br t, J=6Hz), 6.93-7.11 (3H, m), 7.24-7.42 (6H, m), 7.53 (2H, d, J=7.5Hz)

13) 5-Methyl-3-(4-methylphenyl)-N-phenylbenzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.45 (3H, s), 7.09-

7.15 (1H, m), 7.29-7.63 (11H, m), 8.28 (1H, s)

14) 5-Methyl-3-(4-methylphenyl)-N-(2-phenylethyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.44 (3H, s), 2.90 (2H, t, J=7Hz), 3.68 (2H, q, J=7Hz), 6.56 (1H, br t, J=7Hz), 7.18-7.50 (12H, m)

15) N-Furfuryl-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.44 (6H, s), 4.60 (2H, d, J=6Hz), 6.26-6.29 (1H, m), 6.52-6.54 (1H, m), 6.83 (1H, br t, J=6Hz), 7.25-7.55 (8H, m).
MASS (m/z) : 346 (M^++1)

16) 3-(4-Chlorophenyl)-5-methyl-N-(3-methylbutyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.94 (6H, d, J=7Hz), 1.50 (2H, q, J=7Hz), 1.60-1.73 (1H, m), 2.44 (3H, s), 3.44 (2H, q, J=7Hz), 6.58 (1H, br t, J=7Hz), 7.29-7.61 (7H, m)

17) 5-Methyl-N-(3-methylbutyl)-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7Hz), 1.45 (2H, q, J=7Hz), 1.52-1.67 (1H, m), 2.42 (3H, s), 2.43 (3H, s), 3.41 (2H, q, J=7Hz), 6.45 (1H, br t, J=7Hz), 7.25-7.53 (7H, m)

18) 5-Methyl-N-(4-dimethylaminobenzyl)-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.43 (3H, s), 2.96 (6H, s), 4.49 (2H, d, J=6Hz), 6.72 (3H, d, J=7.5Hz), 7.19-7.38 (7H, m), 7.55 (2H, d, J=7.5Hz)

19) N-(2-Chlorobenzyl)-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.44 (6H, s), 4.69 (2H, d, J=6Hz), 6.95 (1H, t, J=6Hz), 7.22-7.53 (11H, m)

20) N-Cyclopentyl-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 1.42-1.50 (2H, m), 1.59-1.65 (4H, m), 1.95-2.05 (2H, m), 2.44 (3H, s), 2.45 (3H, s), 4.37 (1H, sextet, J=7.5Hz), 6.40 (1H, d, J=7.5Hz), 7.23-7.54 (7H, m)

21) N-Cyclopropyl-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.56-0.62 (2H, m), 0.79-0.86 (2H, m), 2.44 (3H, s), 2.45 (3H, s), 2.82-2.89 (1H, m), 6.60 (1H, s), 7.25-7.55 (7H, m)

22) N-(4-Fluorobenzyl)-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.45 (6H, s), 4.57 (2H, d, J=6Hz), 6.80 (1H, t, J=6Hz), 6.99-7.05 (2H, m), 7.25-7.41 (7H, m), 7.53 (2H, d, J=7.5Hz)

23) 5-Methyl-3-(4-methylphenyl)-N-propylbenzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.55-1.63 (2H, m), 2.44 (3H, s), 2.45 (3H, s), 3.38 (2H, q, J=7Hz), 6.52 (1H, br t, J=7Hz), 7.24-7.55 (7H, m)

24) 5-Methyl-3-(4-methylphenyl)-N-pentylbenzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.32 (4H, br s), 1.51-1.57 (2H, m), 2.45 (3H, s), 2.46 (3H,

s), 3.40 (2H, q, J=7Hz), 6.48 (1H, t, J=7Hz), 7.24-7.55 (7H, m)

25) N-Hexyl-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (6H, br s), 1.50-1.55 (2H, m), 2.43 (3H, s), 2.44 (3H, s), 3.39 (2H, q, J=6Hz), 6.48 (1H, t, J=6Hz), 7.24-7.54 (7H, m)

26) N-Butyl-5-methyl-3-(4-methylphenyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.93 (3H, t, J=7Hz), 1.36 (2H, sext, J=7Hz), 1.49-1.58 (2H, m), 2.42 (3H, s), 2.43 (3H, s), 3.40 (2H, q, J=6Hz), 6.49 (1H, t, J=6Hz), 7.23-7.53 (7H, m)

27) N-(2-Chlorobenzyl)-3-(4-chlorophenyl)-5-methylbenzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.72 (2H, d, J=6Hz), 7.07 (1H, t, J=6Hz), 7.22-7.62 (11H, m)

28) 5-Methyl-3-(4-methylphenyl)-N-(2,2-dimethylpropyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.90 (9H, s), 2.42 (6H, s), 3.20 (2H, d, J=7Hz), 6.47 (1H, br t, J=7Hz), 7.23-7.51 (7H, m)

29) 3-(4-Chlorophenyl)-5-methyl-N-(2,2-dimethylpropyl)benzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.97 (9H, s), 2.45 (3H, s), 3.24 (2H, d, J=7Hz), 6.65 (1H, br t, J=7Hz), 7.28-7.60 (7H, m)

30) 3-(4-Bromophenyl)-N-butyl-5-methylbenzofuran-2-

carboxamide

NMR ($CDCl_3$, δ) : 0.96 (3H, t, J=7Hz), 1.40 (2H, sextet, J=7Hz), 1.55-1.65 (2H, m), 2.42 (3H, s), 3.42 (2H, q, J=7Hz), 6.62 (1H, br t, J=7Hz), 7.29-7.43 (3H, m), 7.57 (4H, AB, J=8, 7.5Hz)

Preparation 3

To a solution of butylamine (0.33 g) and triethylamine (0.7 ml) in methylene chloride (10 ml) was added dropwise a solution of 3-(4-chlorophenyl)-5-methyl-2-benzofurancarbonyl chloride (1.13 g) in methylene chloride (10 ml) at 0°C with stirring. The mixture was stirred at ambient temperature for 30 minutes. The mixture was washed with 1N aqueous hydrochloric acid (20 ml x 2) and 5% aqueous sodium bicarbonate (20 ml). The organic layer was dried. Evaporation of solvent gave a residue which was recrystallized from ethyl acetate - n-hexane to afford N-butyl-3-(4-chlorophenyl)-5-methylbenzofuran-2-carboxamide (1.01 g).

NMR ($CDCl_3$, δ) : 0.95 (3H, t, J=7Hz), 1.41 (2H, m), 1.59 (2H, m), 2.44 (3H, s), 3.43 (2H, q, J=7Hz), 6.63 (1H, t, J=7Hz), 7.34 (1H, d, J=2Hz), 7.37 (1H, dd, J=2, 8Hz), 7.43 (1H, d, J=8Hz), 7.46 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz)

Preparation 4

The following compounds were obtained according to a similar manner to that of Preparation 3.

1) 3-(4-Chlorophenyl)-N-hexyl-5-methylbenzofuran-2-carboxamide

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.33 (6H, m), 1.60 (2H, m), 2.43 (3H, s), 3.42 (2H, q, J=7Hz), 6.63 (1H, t, J=7Hz), 7.27 (1H, dd, J=2, 8Hz), 7.34 (1H, d, J=2Hz), 7.42 (1H, d, J=8Hz), 7.45

(2H, d, J=8Hz), 7.60 (2H, d, J=8Hz)

2) 3-(4-Chlorophenyl)-N-(2,2,3,3,4,4,4-heptafluorobutyl)-5-methylbenzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.19 (2H, dt, J=7, 15Hz), 6.87 (1H, t, J=7Hz), 7.32 (1H, dd, J=2, 8Hz), 7.37 (1H, d, J=2Hz), 7.46 (1H, d, J=8Hz), 7.49 (2H, d, J=8Hz), 7.59 (2H, d, J=8Hz)

Preparation 5

To a stirred suspension of aluminum hydride (prepared from aluminum chloride (0.38 g) and lithium aluminum hydride (0.32 g)) in tetrahydrofuran (30 ml) was added N-(4-benzyloxybenzyl)-3-(4-chlorophenyl)-5-methylbenzofuran-2-carboxamide (3.1 g) at 0°C and the mixture was refluxed for 2 hours. After cooling, excess aluminum hydride was destroyed with ice water. The inorganic material was filtered off and washed with diethyl ether. The combined filtrate was washed with water and dried. Evaporation of solvent gave a residue which was purified by column chromatography on silica gel. Elution with chloroform gave N-(4-benzyloxybenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine (1.7 g).

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.70 (2H, s), 3.93 (2H, s), 5.05 (2H, s), 6.87 (2H, d, J=8Hz), 7.13 (2H, d, J=8Hz), 7.34-7.42 (12H, m)

Preparation 6

The following compounds were obtained according to a similar manner to that of Preparation 5.

1) N-(2-Fluorobenzyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.43 (6H, s), 3.84 (2H, s), 4.00 (2H, s), 6.95-7.41 (11H, m)

2) N-Heptyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.23 (8H, br s), 1.39-1.50 (2H, m), 2.41 (3H, s), 2.42 (3H, s), 2.59 (2H, t, J=7Hz), 4.00 (2H, s), 7.08-7.13 (1H, m), 7.30-7.41 (6H, m)

3) N-Cyclobutyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 1.61-1.69 (4H, m), 2.03-2.10 (2H, m), 2.44 (3H, s), 2.45 (3H, s), 3.22-3.32 (1H, m), 3.91 (2H, s), 7.08-7.12 (1H, m), 7.32-7.41 (6H, m)

4) N-(4-Methylbenzyl)-[5-methyl-3-(4-methylphenyl)-benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.33 (3H, s), 2.45 (6H, s), 3.74 (2H, s), 4.00 (2H, s), 7.06-7.16 (6H, m), 7.24-7.40 (5H, m)

5) N-(4-Chlorobenzyl)-[5-methyl-3-(4-methylphenyl)-benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.45 (6H, s), 3.73 (2H, s), 3.99 (2H, s), 7.09-7.40 (11H, m)

6) N-(4-Dimethylaminobenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 2.94 (6H, s), 3.69 (2H, s), 3.94 (2H, s), 6.65 (2H, d, J=7.5Hz), 7.07-7.13 (3H, m), 7.33-7.43 (6H, m)

7) N-Butyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]-methylamine
NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.22-1.48 (4H, m), 2.43 (3H, s), 2.60 (2H, t, J=7Hz), 3.95 (2H,

s), 7.12 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.45 (4H, s)

8) N-Hexyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]-methylamine
NMR ($CDCl_3$, δ) : 0.86 (3H, t, J=7Hz), 1.25 (6H, m), 1.44 (2H, m), 2.42 (3H, s), 2.57 (2H, t, J=7Hz), 3.95 (2H, s), 7.12 (1H, dd, J=2, 8Hz), 7.31 (1H, d, J=2Hz), 7.39 (1H, d, J=8Hz), 7.44 (4H, s)

9) N-(2,2,3,3,4,4,4-Heptafluorobutyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 1.83 (1H, t, J=7Hz), 2.43 (3H, s), 3.26 (2H, dt, J=7, 15Hz), 4.06 (2H, d, J=7Hz), 7.15 (1H, dd, J=2, 8Hz), 7.33 (1H, d, J=2Hz), 7.40 (1H, d, J=8Hz), 7.43 (2H, d, J=8Hz), 7.48 (2H, d, J=8Hz)

10) N-(2-Methylpropyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7Hz), 1.71 (2H, septet, J=7Hz), 2.40 (2H, d, J=7Hz), 2.45 (3H, s), 3.96 (2H, s), 7.12 (1H, dd, J=7.5, 1Hz), 7.32-7.40 (2H, m), 7.47 (4H, s)

11) N-(2-Methylpropyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7Hz), 1.71 (1H, septet, J=7Hz), 2.40 (2H, d, J=7Hz), 2.43 (3H, s), 2.44 (3H, s), 3.98 (2H, s), 7.10 (1H, d, J=7.5Hz), 7.29-7.41 (6H, m)

12) N-(2-Thienylmethyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.44 (6H, s), 3.98 (2H, s), 4.02

(2H, s), 6.75-6.78 (1H, m), 6.87-6.90 (1H, m), 7.11 (1H, d, J=7.5Hz), 7.20 (1H, d, J=5Hz), 7.28 (1H, d, J=7.5Hz), 7.35-7.40 (4H, m)

13) N-(3-Chlorobenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.46 (3H, s), 3.77 (2H, s), 3.96 (2H, s), 7.09-7.25 (5H, m), 7.35-7.47 (6H, m)

14) N-(3-Chlorobenzyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.44 (6H, s), 3.22 (2H, s), 3.98 (2H, s), 7.07-7.39 (11H, m)

15) N-(3-Fluorobenzyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.44 (6H, s), 3.75 (2H, s), 3.99 (2H, s), 6.87-7.00 (3H, m), 7.10-7.29 (4H, m), 7.32-7.40 (4H, m)

16) N-Phenyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.44 (3H, s), 4.48 (2H, s), 6.60-6.63 (2H, m), 6.69-6.75 (1H, m), 7.10-7.16 (3H, m), 7.29-7.40 (6H, m)

17) N-(2-Phenylethyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.44 (3H, s), 2.74-2.90 (4H, m), 4.00 (2H, s), 7.09-7.38 (12H, m)

18) N-Furfuryl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.44 (6H, s), 3.78 (2H, s), 3.99 (2H, s), 6.00-6.02 (1H, m), 6.75-6.78 (1H, m),

7.12 (1H, d, J=7.5Hz), 7.28-7.39 (7H, m)

19) N-(3-Methylbutyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.85 (6H, d, J=7.5Hz), 1.36 (2H, q, J=7.5Hz), 1.55-1.62 (1H, m), 2.44 (3H, s), 2.61 (2H, t, J=7.5Hz), 3.97 (2H, s), 7.12 (1H, d, J=7.5Hz), 7.31-7.48 (6H, m)

20) N-(3-Methylbutyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.83 (6H, d, J=7.5Hz), 1.35 (2H, q, J=7.5Hz), 1.55-1.62 (1H, m), 2.44 (3H, s), 2.45 (3H, s), 2.61 (2H, t, J=7.5Hz), 3.99 (2H, s), 7.10 (1H, d, J=7.5Hz), 7.30-7.41 (6H, m)

21) N-(4-Dimethylaminobenzyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.43 (6H, s), 2.93 (6H, s), 3.69 (2H, s), 3.97 (2H, s), 6.66 (2H, d, J=8.5Hz), 7.10 (3H, d, J=8.5Hz), 7.25-7.39 (6H, m)

22) N-(2-Chlorobenzyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.45 (6H, s), 3.89 (2H, s), 4.00 (2H, s), 7.10-7.25 (4H, m), 7.29-7.40 (7H, m)

23) N-Cyclopentyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 1.26-1.38 (2H, m), 1.46-1.51 (2H, m), 1.63-1.79 (4H, m), 2.43 (3H, s), 2.44 (3H, s), 3.08 (1H, quint, J=7Hz), 3.97 (2H, s), 7.10 (1H, d, J=7.5Hz), 7.29-7.42 (6H, m)

24) N-Cyclopropyl-[5-methyl-3-(4-methylphenyl)benzofuran-

2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.36-0.40 (4H, m), 2.14-2.19 (1H, m), 2.42 (3H, s), 2.44 (3H, s), 4.04 (2H, s), 7.10 (1H, d, J=7.5Hz), 7.29-7.43 (6H, m)

25) N-(4-Fluorobenzyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.45 (6H, s), 3.71 (2H, s), 3.99 (2H, s), 6.90-6.95 (2H, m), 7.10-7.19 (4H, m), 7.29-7.39 (5H, m)

26) N-Propyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7.5Hz), 1.48 (2H, sext, J=7.5Hz), 2.43 (3H, s), 2.44 (3H, s), 2.59 (2H, t, J=7.5Hz), 3.99 (2H, s), 7.10 (1H, d, J=7.5Hz), 7.29-7.40 (6H, m)

27) N-Pentyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.22-1.29 (4H, m), 1.45 (2H, quint, J=7Hz), 2.43 (3H, s), 2.44 (3H, s), 2.59 (2H, t, J=7Hz), 3.99 (2H, s), 7.10 (1H, d, J=7.5Hz), 7.29-7.40 (6H, m)

28) N-Hexyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.86 (3H, t, J=7Hz), 1.23 (6H, br s), 1.40-1.47 (2H, m), 2.44 (3H, s), 2.45 (3H, s), 2.59 (2H, t, J=7.5Hz), 3.99 (2H, s), 7.10 (1H, d, J=7.5Hz), 7.27-7.40 (6H, m)

29) N-Butyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.26-1.35 (2H,

m), 1.38-1.47 (2H, m), 2.33 (3H, s), 2.34 (3H, s), 2.61 (2H, t, J=7Hz), 3.97 (2H, s), 7.11 (1H, d, J=7.5Hz), 7.28-7.41 (6H, m)

30) N-(2-Chlorobenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.90 (2H, s), 3.97 (2H, s), 7.11-7.38 (7H, m), 7.43 (4H, s)

31) N-(2,2-Dimethylpropyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.88 (9H, s), 2.33 (2H, s), 2.44 (6H, s), 3.97 (2H, s), 7.10 (1H, dd, J=7.5, 1Hz), 7.29-7.44 (6H, m)

32) N-(2,2-Dimethylpropyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.89 (9H, s), 2.33 (2H, s), 2.45 (3H, s), 3.96 (2H, s), 7.12 (1H, dd, J=7.5, 1Hz), 7.32-7.51 (6H, m)

33) N-Butyl-[3-(4-bromophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.31 (2H, sextet, J=7Hz), 1.45 (2H, quint, J=7Hz), 2.46 (3H, s), 2.60 (2H, t, J=7Hz), 3.56 (2H, s), 7.12 (1H, dd, J=8, 1Hz), 7.30-7.39 (2H, m), 7.50 (4H, AB, J=8, 8Hz)

Preparation 7

To a stirred solution of ethyl trifluoroacetate (3.035 g) in diethyl ether (4 ml) was added dropwise a solution of 2-(methylthio)ethylamine (1.948 g) in diethyl ether (1 ml) at 0°C. The reaction mixture was stirred at ambient temperature for 19 hours. The reaction mixture

was extracted with ethyl acetate, washed with water, and dried. Evaporation of solvent gave 2,2,2-trifluoro-N-(2-methylthioethyl)acetamide (3.99 g).

IR (Neat) : 1700 cm^{-1}

NMR ($CDCl_3$, δ) : 2.15 (3H, s), 2.71 (2H, t, J=7Hz), 3.59 (2H, q, J=7Hz)

Preparation 8

The following compounds were obtained according to a similar manner to that of Preparation 7.

1) 2,2,2-Trifluoro-N-(2-methoxyethyl)acetamide

IR (Neat) : 1700 cm^{-1}

NMR ($CDCl_3$, δ) : 3.40 (3H, s), 3.50-3.58 (4H, m)

2) 2,2,2-Trifluoro-N-(cyclopropylmethyl)acetamide

NMR ($CDCl_3$, δ) : 0.29 (2H, q, J=7.5Hz), 0.60 (2H, q, J=7.5Hz), 0.96-1.05 (1H, m), 3.23 (2H, t, J=7.5Hz)

Preparation 9

To a stirred suspension of 60% sodium hydride (353 mg) in N,N-dimethylformamide (5 ml) was added dropwise a solution of 2,2,2-trifluoroacetamide (1.0 g) in N,N-dimethylformamide (10 ml) at ambient temperature. The reaction mixture was stirred at ambient temperature for 1.5 hours. To this was added dropwise a solution of 4-bromo-1-butene (1.25 g) in N,N-dimethylformamide (5 ml) at ambient temperature. The reaction mixture was stirred at ambient temperature for 5.5 hours. The solvent was evaporated off. The residue was taken up in ethyl acetate, washed with 1N hydrochloric acid, aqueous diluted sodium bicarbonate and water, and dried. Evaporation of solvent gave an oil which was purified by flash chromatography on silica gel. Elution with a mixture of

ethyl acetate and n-hexane (1:10) gave N-(3-butenyl)-2,2,2-trifluoroacetamide (265 mg).

NMR ($CDCl_3$, δ) : 2.35 (2H, q, J=7.5Hz), 3.46 (2H, q, J=7.5Hz), 5.11-5.18 (2H, m), 5.68-5.83 (1H, m)

Preparation 10

The following compound was obtained according to a similar manner to that of Preparation 9.

N-[(E)-2-Butenyl]-2,2,2-trifluoroacetamide

NMR ($CDCl_3$, δ) : 1.73 (3H, dd, J=7, 1Hz), 3.92 (2H, t, J=7Hz), 5.42-5.53 (1H, m), 5.69-5.79 (1H, m)

Preparation 11

To a stirred suspension of 60% sodium hydride (85 mg) in N,N-dimethylformamide (1 ml) was added dropwise a solution of 2,2,2-trifluoro-N-(2-methylthioethyl)acetamide (377 mg) in N,N-dimethylformamide (2.5 ml) at ambient temperature. The reaction mixture was stirred at ambient temperature for 1.5 hours. To this was added dropwise a solution of 2-chloromethyl-3-(4-chlorophenyl)-5-methylbenzofuran (650 mg) in N,N-dimethylformamide (4 ml) at ambient temperature. The reaction mixture was stirred at ambient temperature for 1 hour. The solvent was evaporated off. The residue was taken up in ethyl acetate, washed with 1N hydrochloric acid, aqueous diluted sodium bicarbonate, water and brine, and dried. Evaporation of solvent gave an oil which was purified by flash chromatography on silica gel. Elution with a mixture of ethyl acetate and n-hexane (1:20) gave N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-2,2,2-trifluoro-N-(2-methylthioethyl)acetamide (688 mg).

NMR ($CDCl_3$, δ) : 1.91 and 2.00 (total 3H, s and s), 2.41-2.56 (2H, m), 2.44 (3H, s), 3.42-3.60 (2H, m), 4.87 and 4.90 (total 2H, s and s), 7.19 (1H,

t, J=7.5Hz), 7.30-7.52 (6H, m)

Preparation 12

The following compounds were obtained according to a similar manner to that of Preparation 11.

1) 2,2,2-Trifluoro-N-[5-methyl-3-(4-methylphenyl)-benzofuran-2-ylmethyl]-N-(2-methylthioethyl)acetamide
NMR ($CDCl_3$, δ) : 1.87 and 1.92 (total 3H, s and s), 2.38-2.49 (2H, m), 2.46 (6H, s), 3.40-3.52 (2H, m), 4.88 and 4.93 (total 2H, s and s), 7.14-7.19 (1H, m), 7.35 (3H, s), 7.36-7.40 (3H, m)

2) 2,2,2-Trifluoro-N-(2-methoxyethyl)-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]acetamide
NMR ($CDCl_3$, δ) : 2.45 (6H, s), 3.11 and 3.16 (total 3H, s and s), 3.38-3.59 (4H, m), 4.42 and 4.50 (total 2H, s and s), 7.14 (1H, t, J=7.5Hz), 7.29-7.42 (6H, m)

3) N-(3-Butenyl)-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-2,2,2-trifluoroacetamide
NMR ($CDCl_3$, δ) : 2.03-2.26 (2H, m), 2.44 (3H, s), 3.30-3.45 (2H, m), 4.78 and 4.88 (total 2H, s and s), 4.84-5.04 (2H, m), 5.43-5.64 (1H, m), 7.18 (1H, t, J=7.5Hz), 7.29-7.52 (6H, m)

4) N-(3-Butenyl)-2,2,2-trifluoro-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]acetamide
NMR ($CDCl_3$, δ) : 2.00-2.18 (2H, m), 2.43 (3H, s), 2.44 (3H, s), 3.27-3.38 (2H, m), 4.79 and 4.90 (total 2H, s and s), 4.81-4.99 (2H, m), 5.40-5.57 (1H, m), 7.16 (1H, t, J=7.5Hz), 7.30-7.40 (6H, m)

5) N-[3-(Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-2,2,2-trifluoro-N-(2-methoxyethyl)acetamide
NMR ($CDCl_3$, δ) : 2.45 (3H, s), 3.15 and 3.20 (total 3H, s and s), 3.41-3.67 (4H, m), 4.93 and 5.00 (total 2H, s and s), 7.17 (1H, t, J=7.5Hz), 7.30-7.41 (3H, m), 7.48 (3H, s)

Preparation 13

To a stirred solution of N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-2,2,2-trifluoro-N-(2-methylthioethyl)acetamide (674 mg) in ethanol (10 ml) was added 1N aqueous sodium hydroxide (2.3 ml) at ambient temperature. The reaction mixture was refluxed for 2 hours. After cooling, ethanol was evaporated off. The residue was taken up in ethyl acetate, washed with 1N aqueous sodium hydroxide, and dried. Evaporation of solvent gave an oil which was purified by flash chromatography on silica gel. Elution with a mixture of ethyl acetate and n-hexane (1:6) gave N-(2-methylthioethyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine (440 mg).

NMR ($CDCl_3$, δ) : 2.05 (3H, s), 2.43 (3H, s), 2.63 (2H, t, J=7Hz), 2.72 (2H, t, J=7Hz), 3.99 (2H, s), 7.12 (1H, dd, J=7.5, 1Hz), 7.30-7.40 (2H, m), 7.47 (4H, s)

Preparation 14

The following compounds were obtained according to a similar manner to that of Preparation 13.

1) N-(2-Methylthioethyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.05 (3H, s), 2.43 (3H, s), 2.44 (3H, s), 2.62 (2H, t, J=7Hz), 2.71 (2H, t, J=7Hz), 4.03 (2H, s), 7.11 (1H, d, J=7.5Hz),

7.29-7.41 (6H, m)

2) N-(2-Methoxyethyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.44 (3H, s), 2.80 (2H, t, J=7Hz), 3.33 (3H, s), 3.47 (2H, t, J=7Hz), 4.01 (2H, s), 7.09 (1H, d, J=7.5Hz), 7.28-7.40 (6H, m)

3) N-(3-Butenyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.23 (2H, q, J=7Hz), 2.45 (3H, s), 2.69 (2H, t, J=7Hz), 3.96 (2H, s), 5.00-5.08 (2H, m), 5.67-5.81 (1H, m), 7.12 (1H, dd, J=8, 1Hz), 7.31 (1H, s), 7.38 (1H, d, J=8Hz), 7.47 (4H, s)

4) N-(3-Butenyl)-[5-methyl-3-(4-methylphenyl)benzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.22 (2H, q, J=7.5Hz), 2.42 (3H, s), 2.43 (3H, s), 2.68 (2H, t, J=7.5Hz), 4.00 (2H, s), 4.99-5.08 (2H, m), 5.66-5.80 (1H, m), 7.10 (1H, dd, J=7.5, 1Hz), 7.29-7.40 (6H, m)

5) N-(2-Methoxyethyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 2.79 (2H, t, J=7Hz), 3.33 (3H, s), 3.49 (2H, t, J=7Hz), 3.99 (2H, s), 7.12 (1H, dd, J=7.5, 1Hz), 7.30 (1H, d, J=1Hz), 7.38 (1H, d, J=7.5Hz), 7.46 (4H, s)

Preparation 15

To a stirred solution of 2,2,2-trifluoro-N-(cyclopropylmethyl)acetamide (559 mg) in 1,3-dimethyl-2-imidazolidinone (2 ml) was added sodium hydroxide (250

mg), anhydrous potassium carbonate (425 mg) and sodium iodide (230 mg). To this mixture was added a solution of 2-chloromethyl-3-(4-chlorophenyl)-5-methylbenzofuran (890 mg) in 1,3-dimethyl-2-imidazolidinone (4 ml) at 0°C and the mixture was stirred for 2 hours at ambient temperature. To this was added 24% aqueous sodium hydroxide (0.55 ml) and stirred for 8 hours. Water (15 ml) was added to the reaction mixture and extracted with ethyl acetate (20 ml). The organic layer was washed with water (15 ml) for three times and brine (15 ml), and dried. Evaporation of the solvent gave a residue which was dissolved in methanol (5 ml). To this solution was added 10% hydrogen chloride in methanol solution (4 ml). Methanol was evaporated to give a residue. Recrystallization from diethyl ether gave N-cyclopropylmethyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine hydrochloride (800 mg).

NMR (CD_3OD, δ) : 0.37 (2H, q, J=7Hz), 0.67 (2H, q, J=7Hz), 1.00-1.10 (1H, m), 2.45 (3H, s), 2.95 (2H, d, J=7Hz), 4.50 (2H, s), 7.28 (1H, dd, J=8, 1Hz), 7.40 (1H, s), 7.49-7.60 (5H, m)

Preparation 16

The following compounds were obtained according to a similar manner to that of Preparation 15.

1) N-Cyclopropylmethyl-[5-methyl-3-(4-methylphenyl)-benzofuran-2-yl]methylamine hydrochloride

NMR (CD_3OD, δ) : 0.35 (2H, q, J=7Hz), 0.66 (2H, q, J=7Hz), 0.99-1.06 (1H, m), 2.44 (6H, s), 2.94 (2H, d, J=7.5Hz), 4.49 (2H, s), 7.26 (1H, dd, J=7.5, 1Hz), 7.37-7.50 (6H, m)

2) N-[(E)-2-Butenyl]-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine hydrochloride

NMR (CD_3OD, δ) : 1.69 (3H, d, J=7Hz), 2.44 (3H, s), 3.59 (2H, d, J=7Hz), 4.43 (2H, s), 5.43-5.52 (1H, m), 5.79-5.91 (1H, m), 7.29 (1H, d, J=7Hz), 7.42 (1H, s), 7.49-7.60 (5H, m)

3) N-[(E)-2-Butenyl]-[5-methyl-3-(4-methylphenyl)-benzofuran-2-yl]methylamine hydrochloride

NMR (CD_3OD, δ) : 1.66 (3H, d, J=7Hz), 2.46 (6H, s), 3.53 (2H, d, J=7Hz), 4.42 (2H, s), 5.40-5.52 (1H, m), 5.73-5.84 (1H, m), 7.27 (1H, d, J=7Hz), 7.38-7.50 (6H, m)

Preparation 17

To a stirred solution of p-cresol (25.0 g) in o-dichlorobenzene (100 ml) was added aluminum chloride (46.2 g) by portions at 40°C. After addition, p-chlorobenzoyl chloride (40.5 g) was added dropwise to the mixture at the same temperature and the mixture was heated at 135°C for 2 hours. After cooling, the reaction mixture was poured into ice-water (100 ml) and the organic layer was separated. The organic layer was washed with water and brine, and dried. Evaporation of solvent gave 4'-chloro-2-hydroxy-5-methylbenzophenone (57.6 g).

IR (Nujol)) : 1638, 1615, 1595, 1340, 1250, 1220, 1090 cm^{-1}

NMR ($CDCl_3$, δ) : 2.25 (3H, s), 6.97 (1H, dd, J=8.9, 1.2Hz), 7.30 (1H, s), 7.33 (1H, d, J=8.9Hz), 7.47 (2H, d, J=8.6Hz), 7.62 (2H, d, J=8.6Hz)

Preparation 18

To a stirred solution of 4'-chloro-2-hydroxy-5-methylbenzophenone (57.6 g) in tetrahydrofuran (256 ml) were added sodium iodide (17.3 g), 28% sodium methoxide in methanol (58.85 g) and methyl chloromethylacetate (37.6 g) and the mixture was refluxed for 2 hours. After cooling

to 50°C, 28% sodium methoxide in methanol (53.5 g) was added dropwise thereto and the mixture was refluxed for 1 hour. To the mixture were added water and dichloromethane and the organic layer was separated. The organic layer was washed with water and brine, and evaporated to afford a residue. Recrystallization from a mixture of methanol and water gave methyl 3-(4-chlorophenyl)-5-methylbenzofuran-2-carboxylate (42.9 g).

IR (Nujol) : 1715, 1580, 1290 cm^{-1}

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 3.89 (3H, s), 7.26 (1H, s), 7.25-7.35 (2H, m), 7.40-7.60 (4H, m)

Preparation 19

To a stirred solution of methyl 3-(4-chlorophenyl)-5-methylbenzofuran-2-carboxylate (16.0 g) in tetrahydrofuran (80 ml) was added sodium borohydride (4.03 g) at the temperature below 45°C. Methanol (16 ml) was added thereto at 45°C and the mixture was stirred at the same temperature for 1 hour. After evaporation of solvent, to the residue were added dichloromethane, water and 17.5% hydrochloric acid. The separated organic layer was washed with water and brine, dried and evaporated to afford 3-(4-chlorophenyl)-2-hydroxy-5-methylbenzofuran (14.5 g).

IR (Nujol) : 3150, 1280, 1185, 1020, 990 cm^{-1}

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.77 (2H, s), 7.16 (1H, dd, J=8.5, 1.5Hz), 7.37 (1H, s), 7.40 (1H, d, J=8.5Hz), 7.48 (4H, s)

Preparation 20

To a stirred solution of benzylamine (9.27 g) and triethylamine (9.63 g) in dichloromethane (46.4 ml) was added dropwise trifluoroacetic anhydride (20.0 g) at 15°C-25°C. After addition, evaporation of solvent gave a residue, which was dissolved with dichloromethane. The solution was washed with water and evaporated to afford

N-benzyltrifluroacetamide (16.3 g).

IR (Nujol) : 3280, 3090, 1690, 1550, 1160 cm^{-1}

NMR ($CDCl_3$, δ) : 4.50 (1H, s), 4.53 (1H, s), 6.69 (1H, br s), 7.25-7.45 (5H, m)

Preparation 21

1) To a stirred solution of 3-(4-chlorophenyl)-2-hydroxymethyl-5-methylbenzofuran (4.53 g) in dichloromethane (23 ml) was added dropwise thionyl chloride (1.98 g) at 20°C-30°C and the mixture was stirred at the same temperature for 30 minutes. Evaporation of solvent gave a residue, to which toluene was added, and further evaporation of solvent gave 2-chloromethyl-3-(4-chlorophenyl)-5-methylbenzofuran.

2) To a stirred solution of N-benzyltrifluoroacetamide (3.72 g) in 1,3-dimethyl-2-imidazolidinone (23 ml) were added sodium hydroxide (1.33 g), potassium carbonate (2.30 g) and sodium iodide (1.15 g). To the mixture was added dropwise a solution of the obtained above 2-chloromethyl-3-(4-chlorophenyl)-5-methylbenzofuran in 1,3-dimethyl-2-imidazolidinone (23 ml) at 30°C. The mixture was stirred at the same temperature for 1 hour to afford the reaction mixture containing N-benzyl-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]trifluoroacetamide. To the reaction mixture was added sodium hydroxide (2.79 g) and the mixture was stirred at 20°C-30°C for 4 hours. After addition of water, the mixture was extracted with ethyl acetate. The organic layer was washed with brine and evaporated to afford N-benzyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine. To a stirred solution of N-benzyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine in toluene (23 ml) was added dropwise 2N hydrochloric acid (23 ml) at the temperature below 30°C and the mixture was stirred at 25°C for 30 minutes.

The precipitate was collected to afford N-benzyl-[(3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine hydrochloride (5.64 g).

IR (Nujol) : 2800-2300, 1570, 1190, 1085 cm^{-1}

NMR (DMSO-d_6, δ) : 2.41 (3H, s), 4.23 (2H, s), 4.31 (2H, s), 7.28 (1H, d, J=8.5Hz), 7.35-7.45 (4H, m), 7.55-7.65 (7H, m), 10.23 (1H, br s)

Preparation 22

To a stirred solution of 3-(4-chlorophenyl)-2-hydroxymethyl-5-methylbenzofuran (1.00 g) in dichloromethane (5 ml) was added dropwise thionyl chloride (0.44 g) at ambient temperature and the mixture was stirred at the same temperature for 30 minutes. Evaporation of solvent gave a residue, to which toluene was added, and further evaporation of solvent gave a residue containing 2-chloromethyl-3-(4-chlorophenyl)-5-methylbenzofuran. To this residue was added benzylamine (10 ml) and the mixture was stirred for 1 hour. After addition of toluene, 35% hydrochloric acid was added to the mixture. The precipitate was collected to afford N-benzyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine hydrochloride (1.11 g).

The spectrum data of this compound coincided with that of the obtained compound in Preparation 21.

Example 1

To a solution of 5-amino-6-methylthioquinoline (0.15 g) in dioxane (10 ml) was added trichloromethyl chloroformate (0.06 ml) at ambient temperature and the reaction mixture was refluxed overnight. To the mixture was added dropwise a solution of N-benzyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine (0.29 g) in dioxane (5 ml) at ambient temperature and the mixture

was stirred at the same temperature for 3 hours. To the mixture was added 1N aqueous sodium hydroxide (1 ml) and the mixture was stirred at ambient temperature for 1 hour. Evaporation of solvent gave a residue which was poured into water (15 ml) and extracted with chloroform (15 ml). The extract was washed with water and dried. Evaporation of solvent gave a residue which was chromatographed on silica gel. Elution with chloroform followed by recrystallization from a mixture of ethyl acetate and n-hexane afforded N-benzyl-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(6-methylthioquinolin-5-yl)urea (0.19 g).

mp : 140°C

NMR ($CDCl_3$, δ) : 2.47 (3H, s), 2.48 (3H, s), 4.59 (2H, s), 4.84 (2H, s), 6.95 (1H, s), 7.12-7.49 (13H, m), 7.68 (1H, d, J=9Hz), 7.99 (1H, d, J=9Hz), 8.12 (1H, dd, J=2, 9Hz), 8.85 (1H, dd, J=2, 5Hz)

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

1) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(6-methylthioquinolin-5-yl)-N-pentylurea

mp : 175-176.5°C

NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.22-1.37 (4H, m), 1.62 (2H, m), 2.45 (3H, s), 2.47 (3H, s), 3.39 (2H, t, J=7Hz), 4.88 (2H, s), 6.83 (1H, s), 7.20 (1H, dd, J=2, 8Hz), 7.33-7.42 (3H, m), 7.46 (4H, s), 7.68 (1H, d, J=9Hz), 7.98 (1H, d, J=9Hz), 8.15 (1H, dd, J=2, 9Hz), 8.84 (1H, dd, J=2, 4Hz)

2) N-Benzyl-N-[[3-(4-chlorophenyl)-5-methylbenzofuran-2-

yl]methyl]-N'-(2,4-dimethylthio-6-methyl-3-pyridyl)urea
mp : 177°C
NMR ($CDCl_3$, δ) : 2.41 (3H, s), 2.44 (3H, s), 2.48 (3H, s), 2.51 (3H, s), 4.50 (2H, s), 4.72 (2H, s), 6.28 (1H, s), 6.65 (1H, s), 7.07-7.45 (12H, m)

3) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(4-methoxybenzyl)urea
mp : 151°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 3.77 (3H, s), 4.41 (2H, s), 4.68 (2H, s), 6.31 (1H, s), 6.66 (1H, s), 6.75 (2H, d, J=8Hz), 6.97 (2H, d, J=8Hz), 7.17 (1H, dd, J=2, 8Hz), 7.31 (1H, d, J=2Hz), 7.36 (2H, d, J=8Hz), 7.40 (1H, d, J=8Hz), 7.45 (2H, d, J=8Hz)

4) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-methoxybenzyl)-N'-(6-methylthioquinolin-5-yl)urea
mp : 164°C
NMR ($CDCl_3$, δ) : 2.46 (6H, s), 3.79 (3H, s), 4.50 (2H, s), 4.82 (2H, s), 6.80 (2H, d, J=8Hz), 7.12 (3H, t, J=8Hz), 7.22 (1H, dd, J=2, 8Hz), 7.35 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.40 (2H, d, J=8Hz), 7.46 (2H, d, J=8Hz), 7.67 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz), 8.84 (1H, dd, J=2, 4Hz)

5) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-pentylurea

mp : 157-158°C

NMR ($CDCl_3$, δ) : 0.82 (3H, t, J=7Hz), 1.20 (4H, m), 1.53 (2H, m), 2.39 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 3.27 (2H, t, J=7Hz), 4.80 (2H, s), 6.03 (1H, s), 6.65 (1H, s), 7.15 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.42 (1H, d, J=8Hz), 7.46 (4H, s)

6) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2-fluorobenzyl)urea

mp : 170°C

NMR ($CDCl_3$, δ) : 2.38 (3H, s), 2.43 (3H, s), 2.48 (3H, s), 2.49 (3H, s), 4.64 (2H, s), 4.78 (2H, s), 6.23 (1H, s), 6.64 (1H, s), 6.96-7.07 (2H, m), 7.15-7.43 (9H, m)

7) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(2-fluorobenzyl)-N'-(6-methylthioquinolin-5-yl)urea

mp : 177°C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.45 (3H, s), 4.72 (2H, s), 4.89 (2H, s), 6.92 (1H, s), 7.06 (2H, t, J=7Hz), 7.17-7.45 (10H, m), 7.66 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz), 8.83 (1H, dd, J=2, 4Hz)

8) N-(4-Benzyloxybenzyl)-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(6-methylthioquinolin-5-yl)urea

mp : 181°C

NMR ($CDCl_3$, δ) : 2.45 (3H, s), 2.46 (3H, s), 4.50 (2H, s), 4.82 (2H, s), 5.05 (2H, s), 6.87 (2H, d, J=8Hz), 7.02 (3H, t, J=8Hz), 7.20 (1H, dd, J=2, 8Hz), 7.34-7.47 (12H, m), 7.68 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz), 8.12 (1H, d,

J=8Hz), 8.85 (1H, dd, J=2, 4Hz)

9) N-(4-Benzyloxybenzyl)-N'-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]urea
mp : 145°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 4.42 (2H, s), 4.70 (2H, s), 5.02 (2H, s), 6.32 (1H, s), 6.66 (1H, s), 6.83 (2H, d, J=8Hz), 6.97 (2H, d, J=8Hz), 7.17 (1H, dd, J=2, 8Hz), 7.31 (1H, d, J=2Hz), 7.33-7.45 (10H, m)

10) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-cyclobutyl-N'-(6-methylthioquinolin-5-yl)urea
mp : 184-185°C
NMR ($CDCl_3$, δ) : 1.68 (2H, m), 2.18 (4H, m), 2.45 (6H, s), 4.42 (1H, m), 4.92 (2H, s), 6.69 (1H, s), 7.18 (1H, dd, J=2, 8Hz), 7.33 (1H, d, J=2Hz), 7.35-7.41 (2H, m), 7.45 (4H, s), 7.68 (1H, d, J=9Hz), 8.01 (1H, dd, J=2, 9Hz), 8.19 (1H, dd, J=2, 9Hz), 8.83 (1H, dd, J=2, 4Hz)

11) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-cyclobutylurea
mp : 174-175°C
NMR ($CDCl_3$, δ) : 1.58 (2H, m), 2.10 (4H, m), 2.38 (3H, s), 2.43 (3H, s), 2.48 (3H, s), 2.49 (3H, s), 4.29 (1H, m), 4.86 (2H, s), 5.93 (1H, s), 6.64 (1H, s), 7.13 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.40 (1H, d, J=8Hz), 7.47 (4H, s)

12) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-

cycloheptylurea
mp : 177-178°C
NMR ($CDCl_3$, δ) : 1.27-1.53 (10H, m), 1.78 (2H, m), 2.38 (3H, s), 2.43 (3H, s), 2.48 (3H, s), 2.49 (3H, s), 4.05 (1H, m), 4.74 (2H, s), 6.39 (1H, s), 6.64 (1H, s), 7.16 (1H, dd, J=2, 8Hz), 7.31 (1H, d, J=2Hz), 7.42 (2H, d, J=8Hz), 7.45 (1H, d, J=8Hz), 7.50 (2H, d, J=8Hz)

13) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-cyclohexylurea
mp : 205-207°C
NMR ($CDCl_3$, δ) : 0.87 (2H, m), 1.04-1.28 (4H, m), 1.52-1.75 (4H, m), 2.39 (3H, s), 2.44 (3H, s), 2.49 (6H, s), 4.02 (1H, m), 4.74 (2H, s), 6.38 (1H, s), 6.64 (1H, s), 7.15 (1H, dd, J=2, 8Hz), 7.31 (1H, d, J=2Hz), 7.42 (2H, d, J=8Hz), 7.44 (1H, d, J=8Hz), 7.50 (2H, d, J=8Hz)

14) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-cyclopentylurea
mp : 185°C
NMR ($CDCl_3$, δ) : 1.46 (6H, br s), 1.84 (2H, m), 2.38 (3H, s), 2.43 (3H, s), 2.48 (3H, s), 2.49 (3H, s), 4.43 (1H, m), 4.75 (2H, s), 6.30 (1H, s), 6.64 (1H, s), 7.14 (1H, dd, J=2, 8Hz), 7.30 (1H, d, J=2Hz), 7.42 (1H, d, J=8Hz), 7.42 (2H, d, J=8Hz), 7.48 (2H, d, J=8Hz)

15) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-cyclopropylurea
mp : 137°C

NMR ($CDCl_3$, δ) : 0.81 (2H, m), 0.92 (2H, m), 2.40 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 2.66 (1H, m), 4.84 (2H, s), 6.59 (1H, s), 6.65 (1H, s), 7.12 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.39 (1H, d, J=8Hz), 7.45 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz)

16) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-propylurea
mp : 212-212.5°C
NMR ($CDCl_3$, δ) : 0.82 (3H, t, J=7Hz), 1.55 (2H, m), 2.40 (3H, s), 2.44 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 3.27 (2H, t, J=7Hz), 4.80 (2H, s), 6.04 (1H, s), 6.65 (1H, s), 7.15 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.42 (1H, d, J=8Hz), 7.46 (4H, s)

17) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-hexylurea
mp : 136°C
NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.20 (6H, m), 1.52 (2H, m), 2.38 (3H, s), 2.43 (3H, s), 2.47 (3H, s), 2.49 (3H, s), 3.27 (2H, t, J=7Hz), 4.80 (2H, s), 6.04 (1H, s), 6.65 (1H, s), 7.16 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.42 (1H, d, J=8Hz), 7.46 (4H, s)

18) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-butyl-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]urea
mp : 177°C
NMR ($CDCl_3$, δ) : 0.82 (3H, t, J=7Hz), 1.24 (2H, m), 1.52 (2H, m), 2.39 (3H, s), 2.43 (3H, s), 2.49

(3H, s), 2.50 (3H, s), 3.30 (2H, t, J=7Hz), 4.80 (2H, s), 6.04 (1H, s), 6.65 (1H, s), 7.16 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.43 (1H, d, J=8Hz), 7.46 (4H, s)

19) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-heptylurea
mp : 133°C
NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.18 (8H, m), 1.52 (2H, m), 2.38 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 3.37 (2H, t, J=7Hz), 4.81 (2H, s), 6.04 (1H, s), 6.66 (1H, s), 7.16 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.42 (1H, d, J=8Hz), 7.46 (4H, s)

20) N-(2-Fluorobenzyl)-N-[5-methyl-3-(4-methylphenyl)-benzofuran-2-ylmethyl)-N'-(6-methylthioquinolin-5-yl)urea
mp : 159.5-161°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.43 (3H, s), 2.45 (3H, s), 4.74 (2H, s), 4.90 (2H, s), 6.91 (1H, s), 6.98-7.08 (2H, m), 7.16-7.45 (10H, m), 7.68 (1H, d, J=9Hz), 8.00 (1H, d, J=10Hz), 8.11 (1H, d, J=10Hz), 8.85 (1H, dd, J=5, 1Hz)
MASS (m/z) : 576 (M^++1)

21) N-Benzyl-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(6-methylthioquinolin-5-yl)urea
mp : 151-153°C
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.45 (3H, s), 2.46 (3H, s), 4.57 (2H, s), 4.85 (2H, s), 7.00 (1H, s), 7.10-7.47 (13H, m), 7.68 (1H, d, J=9Hz), 8.00 (1H, d, J=9Hz), 8.15 (1H, d, J=9Hz), 8.85

(1H, dd, J=5, 1Hz)
MASS (m/z) : 558 (M^++1)

22) N-Heptyl-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(6-methylthioquinolin-5-yl)urea
mp : 164-166°C
NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.20 (8H, br s), 1.50-1.60 (2H, m), 2.42 (3H, s), 2.45 (6H, s), 3.38 (2H, t, J=7Hz), 4.90 (2H, s), 6.90 (1H, s), 7.15-7.20 (1H, m), 7.30-7.46 (7H, m), 7.70 (1H, d, J=9Hz), 7.99 (1H, d, J=9Hz), 8.17 (1H, d, J=9Hz), 8.84 (1H, dd, J=5, 1Hz)
MASS (m/z) : 566 (M^++1)

23) N-Cyclobutyl-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(6-methylthioquinolin-5-yl)urea
mp : 174-175°C
NMR ($CDCl_3$, δ) : 1.58-1.66 (2H, m), 2.04-2.20 (4H, m), 2.40 (3H, s), 2.44 (6H, s), 4.39-4.48 (1H, m), 4.96 (2H, s), 6.78 (1H, s), 7.14-7.43 (8H, m), 7.68 (1H, d, J=9.5Hz), 7.98 (1H, d, J=9.5Hz), 8.18 (1H, d, J=9Hz), 8.84 (1H, dd, J=5, 1Hz)
MASS (m/z) : 522 (M^++1)

24) N-Benzyl-N'-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 147-148°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.43 (6H, s), 2.49 (3H, s), 2.50 (3H, s), 4.47 (2H, s), 4.70 (2H, s), 6.38 (1H, s), 6.67 (1H, s), 7.04-7.45 (12H, m)
MASS (m/z) : 568 (M^++1)

25) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-

heptyl-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 131-132°C
NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 1.14 (8H, br s), 1.40-1.53 (2H, m), 2.42 (3H, s), 2.45 (3H, s), 2.46 (3H, s), 2.57 (6H, s), 3.28 (2H, t, J=7Hz), 4.80 (2H, s), 6.19 (1H, s), 6.69 (1H, s), 7.15 (1H, dd, J=9, 2Hz), 7.30-7.43 (6H, m)
MASS (m/z) : 576 (M^++1)

26) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2-fluorobenzyl)-N'-[5-methyl-3-(4-methylphenyl)-benzofuran-2-ylmethyl]urea
mp : 150-153°C
NMR ($CDCl_3$, δ) : 2.39 (3H, s), 2.41 (3H, s), 2.43 (3H, s), 2.50 (6H, s), 4.67 (2H, s), 4.69 (2H, s), 6.28 (1H, s), 6.65 (1H, s), 6.95-7.43 (11H, m)
MASS (m/z) : 586 (M^++1)

27) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cyclobutyl-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl)urea
mp : 184-187°C
NMR ($CDCl_3$, δ) : 1.46-1.53 (2H, m), 1.94-2.10 (4H, m), 2.39 (3H, s), 2.42 (6H, s), 2.49 (3H, s), 2.50 (3H, s), 4.32 (1H, qui, J=8Hz), 4.88 (2H, s), 6.07 (1H, s), 6.65 (1H, s), 7.13 (1H, dd, J=9, 2Hz), 7.30-7.42 (6H, m)
MASS (m/z) : 532 (M^++1)

28) N-[5-Methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N-(4-methylbenzyl)-N'-(6-methylthioquinolin-5-yl)urea
mp : 159-160°C
NMR ($CDCl_3$, δ) : 2.33 (3H, s), 2.43 (3H, s), 2.45

(3H, s), 2.46 (3H, s), 4.52 (2H, s), 4.83 (2H, s), 6.99-7.10 (5H, m), 7.17-7.22 (1H, m), 7.30-7.48 (7H, m), 7.69 (1H, d, J=9.5Hz), 7.99 (1H, d, J=9.5Hz), 8.11 (1H, d, J=9.5Hz), 8.85 (1H, dd, J=5, 2Hz)

MASS (m/z) : 572 (M^++1)

29) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(4-methylbenzyl)urea

mp : 140-142°C

NMR ($CDCl_3$, δ) : 2.32 (3H, s), 2.41 (3H, s), 2.43 (3H, s), 2.44 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 4.42 (2H, s), 4.69 (2H, s), 6.38 (1H, s), 6.67 (1H, s), 6.94-7.45 (11H, m)

MASS (m/z) : 582 (M^++1)

30) N-(4-Chlorobenzyl)-N-[5-methyl-3-(4-methylphenyl)-benzofuran-2-ylmethyl]-N'-(6-methylthioquinolin-5-yl)urea

mp : 156.5-159.5°C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.45 (3H, s), 2.49 (3H, s), 4.48 (2H, s), 4.79 (2H, s), 7.00 (2H, d, J=9Hz), 7.08 (1H, s), 7.19-7.47 (10H, m), 7.69 (1H, d, J=9.5Hz), 8.01 (1H, d, J=9.5Hz), 8.15 (1H, d, J=10Hz), 8.88 (1H, dd, J=5, 1Hz)

MASS (m/z) : 592 (M^++1)

31) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(4-chlorobenzyl)-N'-[5-methyl-3-(4-methylphenyl)-benzofuran-2-ylmethyl]urea

mp : 150.5-152.5°C

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.44 (3H, s), 2.45 (3H, s), 2.51 (3H, s), 2.53 (3H, s), 4.39 (2H, s), 4.65 (2H, s), 6.48 (1H, s), 6.68 (1H, s),

6.95 (2H, d, J=9Hz), 7.10-7.20 (3H, m), 7.30 (4H, s), 7.35-7.45 (2H, m)

MASS (m/z) : 602 (M^++1)

32) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(4-chlorobenzyl)-N'-[3-(4-chlorophenyl)-5-methyl-benzofuran-2-ylmethyl]urea

mp : 149-150°C

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.45 (3H, s), 2.51 (3H, s), 2.52 (3H, s), 4.42 (2H, s), 4.69 (2H, s), 6.38 (1H, s), 6.68 (1H, s), 6.99 (2H, d, J=8Hz), 7.15-7.49 (9H, m)

MASS (m/z) : 622 (M^+)

33) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-methylbenzyl)-N'-(6-methylthioquinolin-5-yl)urea

mp : 167-170°C

NMR ($CDCl_3$, δ) : 2.34 (3H, s), 2.47 (6H, s), 4.54 (2H, s), 4.84 (2H, s), 6.95 (1H, s), 7.00-7.10 (4H, m), 7.18-7.25 (1H, m), 7.33-7.48 (7H, m), 7.68 (1H, d, J=9.5Hz), 7.99 (1H, d, J=10Hz), 8.10 (1H, d, J=9Hz), 8.84 (1H, dd, J=5, 1Hz)

MASS (m/z) : 592 (M^++1)

34) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(4-methylbenzyl)urea

mp : 168-171°C

NMR ($CDCl_3$, δ) : 2.31 (3H, s), 2.40 (3H, s), 2.44 (3H, s), 2.50 (3H, s), 2.52 (3H, s), 4.47 (2H, s), 4.71 (2H, s), 6.29 (1H, s), 6.66 (1H, s), 6.96-7.47 (11H, m)

mass (m/z) : 602 (M^++1)

35) N-(4-Chlorobenzyl)-N-[3-(4-chlorophenyl)-5-methyl-

benzofuran-2-ylmethyl]-N'-(6-methylthioquinolin-5-yl)urea

mp : 192.5-194°C

NMR ($CDCl_3$, δ) : 2.46 (3H, s), 2.47 (3H, s), 4.51 (2H, s), 4.70 (2H, s), 7.00 (1H, s), 7.03 (1H, d, J=9Hz), 7.20-7.25 (2H, m), 7.33-7.49 (8H, m), 7.68 (1H, d, J=9Hz), 8.01 (1H, d, J=9.5Hz), 8.13 (1H, d, J=9.5Hz), 8.87 (1H, dd, J=5, 1Hz)

MASS (m/z) : 612 (M^+)

36) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(4-fluorobenzyl)urea

mp : 176-178°C

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.45 (3H, s), 2.51 (3H, s), 2.53 (3H, s), 4.43 (2H, s), 4.69 (2H, s), 6.37 (1H, s), 6.68 (1H, s), 6.90 (2H, dd, J=8, 8Hz), 6.99-7.05 (2H, m), 7.16-7.20 (1H, m), 7.31-7.48 (6H, m)

MASS (m/z) : 606 (M^++1)

37) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-fluorobenzyl)-N'-(6-methylthioquinolin-5-yl)urea

mp : 167-168.5°C

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 2.49 (3H, s), 4.52 (2H, s), 4.80 (2H, s), 6.92-7.09 (5H, m), 7.20-7.24 (1H, m), 7.33-7.48 (7H, m), 7.68 (1H, d, J=9Hz), 8.01 (1H, d, J=9Hz), 8.14 (1H, d, J=9Hz), 8.86 (1H, dd, J=4.5, 1.5Hz)

MASS (m/z) : 596 (M^++1)

38) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-dimethylaminobenzyl)-N'-(6-methylthioquinolin-5-yl)urea

mp : 145-148.5°C

NMR ($CDCl_3$, δ) : 2.46 (3H, s), 2.47 (3H, s), 2.94 (6H, s), 4.49 (2H, s), 4.85 (2H, s), 6.83 (4H, AB, J=9.5, 9.5Hz), 6.97 (1H, s), 7.18-7.23 (1H, m), 7.34-7.49 (7H, m), 7.68 (1H, d, J=9.5Hz), 7.99 (1H, d, J=10Hz), 8.10 (1H, d, J=8Hz), 8.84 (1H, dd, J=5, 1Hz)
MASS (m/z) : 621 (M^++1)

39) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(4-dimethylaminobenzyl)urea
mp : 157-158.5°C
NMR ($CDCl_3$, δ) : 2.41 (3H, s), 2.45 (3H, s), 2.50 (3H, s), 2.51 (3H, s), 2.94 (6H, s), 4.40 (2H, s), 4.71 (2H, s), 6.29 (1H, s), 6.57-6.67 (3H, m), 6.92-6.98 (2H, m), 7.13-7.48 (7H, m)
MASS (m/z) : 631 (M^++1)

40) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(3-fluorobenzyl)-N'-(6-methylthioquinolin-5-yl)urea
mp : 109-110°C
NMR ($CDCl_3$, δ) : 2.47 (3H, s), 2.49 (3H, s), 4.57 (2H, s), 4.85 (2H, s), 6.85-6.97 (3H, m), 6.99 (1H, s), 7.18-7.24 (2H, m), 7.33-7.49 (7H, m), 7.69 (1H, d, J=9Hz), 8.01 (1H, d, J=10Hz), 8.15 (1H, d, J=9.5Hz), 8.87 (1H, dd, J=5, 1Hz)
MASS (m/z) : 596 (M^++1)

41) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(3-fluorobenzyl)urea
mp : 166-168.5°C
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.45 (3H, s), 2.50 (3H, s), 2.54 (3H, s), 4.49 (2H, s), 4.71 (2H, s), 6.34 (1H, s), 6.69 (1H, s), 6.80-6.95 (3H,

m), 7.12-7.48 (8H, m)
MASS (m/z) : 606 (M^++1)

42) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2-chlorobenzyl)-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]urea
mp : 157-158.5°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 4.69 (2H, s), 4.83 (2H, s), 6.18 (1H, s), 6.65 (1H, s), 7.13-7.17 (3H, m), 7.29-7.42 (8H, m)
MASS (m/z) : 622 (M^+)

Example 3

To a stirred solution of N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(4-methoxybenzyl)urea (0.43 g) in methylene chloride (10 ml) was added dropwise boron tribromide (0.3 ml) at 0°C. The reaction mixture was stirred at ambient temperature for 2 hours. The mixture was poured into water. The organic solution was washed with water and dried. Evaporation of solvent gave a residue which was chromatographed on silica gel. Elution with 0.5% methanol-chloroform followed by recrystallization from ethyl acetate gave N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(4-hydroxybenzyl)urea (120 mg).

mp : 270°C
NMR (CD_3OD, δ) : 2.43 (3H, s), 2.44 (3H, s), 2.51 (6H, s), 4.37 (2H, s), 4.68 (2H, s), 6.67 (2H, d, J=8Hz), 6.71 (1H, s), 6.88 (2H, d, J=8Hz), 7.17 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.34-7.48 (5H, m)

Example 4

The following compound was obtained according to a similar manner to that of Example 3.

N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-hydroxybenzyl)-N'-(6-methylthioquinolin-5-yl)urea

mp : 204°C

NMR (DMSO-d_6, δ) : 2.42 (6H, s), 4.52 (2H, s), 4.55 (2H, s), 7.21 (1H, dd, J=2, 8Hz), 7.39 (1H, d, J=2Hz), 7.53-7.71 (9H, m), 7.79 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 8.12-8.19 (2H, m), 8.85 (1H, d, J=4Hz)

Example 5

1) To a stirred solution of 3-amino-2,4-bis(methylthio)-6-methylpyridine (0.1 g) and N,N-dimethylaniline (0.075 g) in methylene chloride (3 ml) was added dropwise phenyl chloroformate (0.08 g) at ambient temperature, and the mixture was stirred at the same temperature for 3 hours. The reaction mixture was washed with 3% aqueous hydrochloric acid (3 ml x 2) and dilute aqueous sodium bicarbonate (3 ml), and dried. Evaporation of solvent followed by recrystallization from ethyl acetate - n-hexane gave 2,4-bis(methylthio)-6-methyl-3-phenoxycarbonylaminopyridine (0.1 g).

NMR ($CDCl_3$, δ) : 2.45 (3H, s), 2.51 (3H, s), 2.55 (3H, s), 6.21 (1H, s), 6.67 (1H, s), 7.12-7.41 (5H, m)

2) A mixture of N-(2-furanylmethyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-yl]methylamine (0.22 g), 2,4-bis(methylthio)-6-methyl-3-phenoxycarbonylaminopyridine (0.2 g) and triethylamine (0.44 ml) in N,N-dimethylformamide (1 ml) was stirred at 50°C for 2 hours. After cooling the reaction mixture was diluted with chloroform

(10 ml). The mixture was washed with 1N hydrochloric acid (10 ml x 3) and dilute aqueous sodium bicarbonate (10 ml), and dried. Evaporation of solvent gave a residue which was recrystallized from ethyl acetate - n-hexane to afford N-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(furan-2-ylmethyl)urea (0.26 g).

mp : 142-143°C

NMR ($CDCl_3$, δ) : 2.38 (3H, s), 2.43 (3H, s), 2.48 (3H, s), 2.50 (3H, s), 4.52 (2H, s), 4.81 (2H, s), 5.99 (1H, d, J=3Hz), 6.22 (1H, dd, J=2, 3Hz), 6.38 (1H, s), 6.65 (1H, s), 7.16 (1H, d, J=7Hz), 7.29 (1H, s), 7.32 (1H, s), 7.41 (1H, d, J=7Hz), 7.41 (2H, d, J=8Hz), 7.45 (2H, d, J=8Hz)

Example 6

The following compounds were obtained according to a similar manner to that of Example 5.

1) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(3-methylbutyl)urea

mp : 148-149°C

NMR ($CDCl_3$, δ) : 0.79 (6H, d, J=7Hz), 1.39-1.50 (3H, m), 2.41 (3H, s), 2.45 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 3.29 (2H, t, J=7.5Hz), 4.79 (2H, s), 6.07 (1H, s), 6.65 (1H, s), 7.16 (1H, d, J=7.5Hz), 7.33 (1H, s), 7.42 (2H, d, J=8Hz), 7.48 (3H, s)

MASS (m/z) : 568 (M^++1)

2) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,2,3,3,4,4,4-heptafluorobutyl)urea

mp : 164.5-165°C

NMR ($CDCl_3$, δ) : 2.34 (3H, s), 2.53 (6H, s), 2.47 (3H, s), 4.13 (2H, t, J=15Hz), 4.88 (2H, s), 6.62 (1H, s), 7.18 (1H, dd, J=2, 8Hz), 7.29 (1H, d, J=2Hz), 7.38 (2H, d, J=8Hz), 7.42 (1H, d, J=8Hz), 7.47 (2H, d, J=8Hz)

3) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2-methylpropyl)urea

mp : 158-160°C

NMR ($CDCl_3$, δ) : 0.85 (6H, d, J=7Hz), 1.85-1.94 (1H, m), 2.39 (3H, s), 2.43 (3H, s), 2.48 (3H, s), 2.50 (3H, s), 3.12 (2H, d, J=7Hz), 4.81 (2H, s), 6.10 (1H, s), 6.65 (1H, s), 7.16 (1H, d, J=7.5Hz), 7.30-7.49 (6H, m)

MASS (m/z) : 554 (M^++1)

4) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2-methylpropyl)urea

mp : 149-151°C

NMR ($CDCl_3$, δ) : 0.80 (6H, d, J=7Hz), 1.80-1.90 (1H, m), 2.40 (3H, s), 2.42 (3H, s), 2.43 (3H, s), 2.47 (3H, s), 2.49 (3H, s), 3.11 (2H, d, J=7Hz), 4.80 (2H, s), 6.21 (1H, s), 6.65 (1H, s), 7.15 (1H, dd, J=7.5, 1Hz), 7.29-7.43 (6H, m)

MASS (m/z) : 534 (M^++1)

5) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2-methylthioethyl)urea

mp : 173-175°C

NMR ($CDCl_3$, δ) : 1.99 (3H, s), 2.39 (3H, s), 2.41 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 2.58 (2H, t, J=7.5Hz), 3.50 (2H, t,

J=7.5Hz), 4.83 (2H, s), 6.46 (1H, s), 6.65 (1H, s), 7.15 (1H, dd, J=7.5, 1Hz), 7.29-7.42 (6H, m)
MASS (m/z) : 552 (M^++1)

6) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl)-N'-(2-methoxyethyl)-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 119-121°C
NMR ($CDCl_3$, δ) : 2.41 (3H, s), 2.42 (3H, s), 2.45 (3H, s), 2.50 (3H, s), 2.53 (3H, s), 3.30 (3H, s), 3.32 (2H, t, J=6Hz), 3.61 (2H, t, J=6Hz), 4.89 (2H, s), 6.65 (1H, s), 7.14 (1H, dd, J=7.5, 1Hz), 7.29-7.44 (6H, m), 7.59 (1H, br s)
MASS (m/z) : 536 (M^++1)

7) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(3-butenyl)-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]urea
mp : 168-169°C
NMR ($CDCl_3$, δ) : 2.29 (2H, q, J=7.5Hz), 2.40 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 3.39 (2H, t, J=7.5Hz), 4.80 (2H, s), 4.96-5.02 (2H, m), 5.62-5.67 (1H, m), 6.09 (1H, s), 6.66 (1H, s), 7.18 (1H, d, J=7.5Hz), 7.32 (1H, s), 7.42 (1H, d, J=7.5Hz), 7.47 (4H, s)
MASS (m/z) : 552 (M^++1)

8) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(3-butenyl)-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 173-175°C
NMR ($CDCl_3$, δ) : 2.25 (2H, q, J=7.5Hz), 2.40 (3H, s), 2.43 (3H, s), 2.44 (3H, s), 2.50 (3H, s), 2.51 (3H, s), 3.37 (2H, t, J=7.5Hz), 4.81 (2H, s), 4.93-4.99 (2H, m), 5.59-5.71 (1H, m), 6.19

(1H, s), 6.65 (1H, s), 7.15 (1H, d, J=7.5Hz), 7.28-7.43 (6H, m)

MASS (m/z) : 532 (M^++1)

9) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2-methylthioethyl)urea

mp : 153-155.5°C

NMR ($CDCl_3$, δ) : 2.04 (3H, s), 2.40 (3H, s), 2.45 (3H, s), 2.50 (3H, s), 2.51 (3H, s), 2.62 (2H, t, J=7.5Hz), 3.56 (2H, t, J=7.5Hz), 4.84 (2H, s), 6.41 (1H, s), 6.65 (1H, s), 7.18 (1H, dd, J=7.5, 1Hz), 7.32 (1H, s), 7.41 (1H, d, J=8Hz), 7.48 (4H, s)

MASS (m/z) : 572 (M^++1)

10) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2-methoxyethyl)urea

mp : 147-148°C

NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.44 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 3.30 (3H, s), 3.36 (2H, t, J=6Hz), 3.66 (2H, t, J=6Hz), 4.87 (2H, s), 6.65 (1H, s), 7.16 (1H, dd, J=7.5, 1Hz), 7.37-7.52 (6H, m), 7.61 (1H, s)

MASS (m/z) : 556 (M^++1)

11) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2-thienylmethyl)urea

mp : 150-151°C

NMR ($CDCl_3$, δ) : 2.39 (3H, s), 2.45 (6H, s), 2.49 (3H, s), 2.50 (3H, s), 4.62 (2H, s), 4.74 (2H, s), 6.39 (1H, s), 6.60-6.62 (1H, m), 6.67 (1H, s), 6.82-6.85 (1H, m), 7.14-7.19 (2H, m),

7.28-7.43 (5H, m)
MASS (m/z) : 574 (M^++1)

12) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2-thienylmethyl)urea
mp : 172-173.5°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.44 (3H, s), 2.48 (3H s), 2.49 (3H, s), 4.67 (2H, s), 4.77 (2H, s), 6.32 (1H, s), 6.67 (1H, s), 6.70 (1H, d, J=4Hz), 6.87 (1H, t, J=4Hz), 7.16-7.20 (1H, m), 7.31-7.49 (7H, m)
MASS (m/z) : 594 (M^++1)

13) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(3-chlorobenzyl)-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]urea
mp : 155-157.5°C
NMR ($CDCl_3$, δ) : 2.41 (3H, s), 2.45 (3H, s), 2.50 (3H, s), 2.53 (3H, s), 4.45 (2H, s), 4.71 (2H, s), 6.38 (1H, s), 6.67 (1H, s), 6.78-6.98 (2H, m), 7.07-7.24 (3H, m), 7.29-7.48 (6H, m)
MASS (m/z) : 622 (M^+)

14) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(3-chlorobenzyl)-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 180-182°C
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.44 (3H, s), 2.46 (3H, s), 2.50 (3H, s), 2.53 (3H, s), 4.38 (2H, s), 4.67 (2H, s), 6.50 (1H, s), 6.69 (1H, s), 6.79-7.01 (3H, m), 7.10-7.24 (3H, m), 7.31 (3H, s), 7.33-7.44 (2H, m)
MASS (m/z) : 602 (M^++1)

15) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(3-fluorobenzyl)-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 199-205.5°C
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.44 (3H, s), 2.45 (3H, s), 2.50 (3H, s), 2.52 (3H, s), 4.42 (2H, s), 4.68 (2H, s), 6.48 (1H, s), 6.66-6.70 (1H, m), 6.68 (1H, s), 6.83-6.91 (2H, m), 7.11-7.19 (2H, m), 7.29-7.45 (6H, m)
MASS (m/z) : 586 (M^++1)

16) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-phenylurea
mp : 173-174°C
NMR ($CDCl_3$, δ) : 2.38 (3H, s), 2.40 (6H, s), 2.47 (3H, s), 2.50 (3H, s), 5.19 (2H, s), 5.50 (1H, s), 6.62 (1H, s), 7.08 (4H, AB, J=8, 7.5Hz), 7.10 (1H, dd, J=7.5, 1Hz), 7.25-7.42 (7H, m)
MASS (m/z) : 554 (M^++1)

17) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2-phenylethyl)urea
mp : 139-142°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.43 (3H, s), 2.46 (3H, s), 2.51 (3H, s), 2.53 (3H, s), 2.81 (2H, t, J=7.5Hz), 2.95 (2H, t, J=7.5Hz), 4.68 (2H, s), 6.26 (1H, s), 6.69 (1H, s), 6.99-7.01 (2H, m), 7.13-7.21 (4H, m), 7.30-7.43 (6H, m)
MASS (m/z) : 582 (M^++1)

18) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-bromophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-furfurylurea

mp : 165-167°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.45 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 4.54 (2H, s), 4.81 (2H, s), 5.98-6.00 (1H, m), 6.21-6.23 (1H, m), 6.39 (1H, s), 6.67 (1H, s), 7.16 (1H, dd, J=7.5, 1Hz), 7.27-7.43 (5H, m), 7.61 (2H, d, J=7.5Hz)
MASS (m/z) : 624 (M^++2)

19) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-phenylurea
mp : 151-154°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.41 (3H, s), 2.48 (3H, s), 2.49 (3H, s), 5.16 (2H, s), 5.49 (1H, s), 6.61 (1H, s), 7.07-7.14 (3H, m), 7.21-7.40 (9H, m)
MASS (m/z) : 574 (M^++1)

20) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2-phenylethyl)urea
mp : 161-163°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.43 (3H, s), 2.50 (3H, s), 2.52 (3H, s), 2.85 (2H, t, J=7.5Hz), 2.97 (2H, t, J=7.5Hz), 4.62 (2H, s), 6.15 (1H, s), 6.68 (1H, s), 7.04 (2H, d, J=7.5Hz), 7.13-7.39 (10H, m)
MASS (m/z) : 602 (M^++1)

21) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-furfuryl-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 155-157.5°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.43 (3H, s), 2.44 (3H, s), 2.50 (6H, s), 4.52 (2H, s), 4.82 (2H,

s), 5.92-5.94 (1H, m), 6.20-6.22 (1H, m), 6.43 (1H, s), 6.66 (1H, s), 7.15 (1H, dd, J=7.5, 1Hz), 7.28-7.43 (7H, m)

MASS (m/z) : 558 (M^++1)

22) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(3-methylbutyl)-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea

mp : 187-189°C

NMR ($CDCl_3$, δ) : 0.77 (6H, d, J=7Hz), 1.34-1.50 (3H, m), 2.40 (3H, s), 2.43 (3H, s), 2.44 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 3.29 (2H, t, J=7Hz), 4.80 (2H, s), 6.19 (1H, s), 6.68 (1H, s), 7.16 (1H, d, J=7.5Hz), 7.29-7.43 (6H, m)

MASS (m/z) : 548 (M^++1)

23) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(4-dimethylaminobenzyl)urea

mp : 149.5-152°C

NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.44 (3H, s), 2.45 (3H, s), 2.47 (3H, s), 2.48 (3H, s), 2.92 (6H, s), 4.39 (2H, s), 4.70 (2H, s), 6.35 (1H, s), 6.65 (1H, s), 6.77 (4H, AB, J=8, 7.5Hz), 7.15 (1H, d, J=7.5Hz), 7.30-7.44 (6H, m)

MASS (m/z) : 611 (M^++1)

24) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(2-chlorobenzyl)-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea

mp : 145-147.5°C

NMR ($CDCl_3$, δ) : 2.39 (6H, s), 2.43 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 4.70 (2H, s), 4.81 (2H, s), 6.23 (1H, s), 6.65 (1H, s), 7.12-7.15 (3H, m), 7.20-7.42 (8H, m)

MASS (m/z) : 602 (M^++1)

25) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cyclopentyl-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 189-191°C
NMR ($CDCl_3$, δ) : 1.42 (6H, br s), 1.27-1.35 (2H, m), 2.39 (3H, s), 2.45 (6H, s), 2.50 (6H, s), 4.49 (1H, br quint, J=7.5Hz), 4.78 (2H, s), 6.44 (1H, s), 6.64 (1H, s), 7.15 (1H, d, J=7.5Hz), 7.27-7.45 (6H, m)
MASS (m/z) : 546 (M^++1)

26) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cyclopropyl-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 109-111°C
NMR ($CDCl_3$, δ) : 0.70-0.78 (2H, m), 0.85-0.90 (2H, m), 2.42 (3H, s), 2.45 (6H, s), 2.50 (3H, s), 2.52 (3H, s), 2.56-2.64 (1H, m), 4.89 (2H, s), 6.61 (1H, s), 6.68 (1H, s), 7.10 (1H, d, J=7.5Hz), 7.28-7.45 (6H, m)
MASS (m/z) : 518 (M^++1)

27) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-(4-flurobenzyl)-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 179-181.5°C
NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.42 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 4.39 (2H, s), 4.65 (2H, s), 6.47 (1H, s), 6.67 (1H, s), 6.82-6.88 (2H, m), 6.94-7.00 (2H, m), 7.16 (1H, d, J=7.5Hz), 7.80 (3H, s), 7.32-7.43 (3H, m)
MASS (m/z) : 586 (M^++1)

28) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-propylurea
mp : 191-193°C
NMR ($CDCl_3$, δ) : 0.79 (3H, t, J=7Hz), 1.46-1.55 (2H, m), 2.40 (3H, s), 2.43 (3H, s), 2.44 (3H, s), 2.50 (3H, s), 2.51 (3H, s), 3.27 (2H, t, J=7Hz), 4.80 (2H, s), 6.15 (1H, s), 6.66 (1H, s), 7.15 (1H, dd, J=7.5, 2Hz), 7.29-7.43 (6H, m)
MASS (m/z) : 520 (M^++1)

29) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-pentylurea
mp : 190-193°C
NMR ($CDCl_3$, δ) : 0.79 (3H, t, J=7Hz), 1.11-1.20 (4H, m), 1.45-1.52 (2H, m), 2.39 (3H, s), 2.43 (3H, s), 2.44 (3H, s), 2.50 (3H, s), 2.51 (3H, s), 3.27 (2H, t, J=7Hz), 4.81 (2H, s), 6.14 (1H, s), 6.65 (1H, s), 7.14 (1H, d, J=7.5Hz), 7.29-7.44 (6H, m)
MASS (m/z) : 548 (M^++1)

30) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-hexyl-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 159-161°C
NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 1.15 (6H, br s), 1.42-1.52 (2H, m), 2.40 (3H, s), 2.44 (3H, s), 2.45 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 3.27 (2H, t, J=7.5Hz), 4.79 (2H, s), 6.15 (1H, s), 6.64 (1H, s), 7.14 (1H, dd, J=7.5, 1Hz), 7.29-7.43 (6H, m)
MASS (m/z) : 562 (M^++1)

31) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-butyl-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea
mp : 183-186°C
NMR ($CDCl_3$, δ) : 0.80 (3H, t, J=7Hz), 1.20 (2H, sextet, J=7Hz), 1.48 (2H, quintet, J=7Hz), 2.39 (3H, s), 2.43 (3H, s), 2.44 (3H, s), 2.49 (3H, s), 2.50 (3H, s), 3.28 (2H, t, J=7Hz), 4.79 (2H, s), 6.17 (1H, s), 6.65 (1H, s), 7.15 (2H, d, J=7.5Hz), 7.29-7.43 (5H, m)
MASS (m/z) : 534 (M^++1)

32) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2,2-dimethylpropyl)urea
mp : 189-190.5°C
NMR ($CDCl_3$, δ) : 0.85 (9H, s), 2.35 (3H, s), 2.41 (6H, s), 2.43 (3H, s), 2.44 (3H, s), 3.16 (2H, s), 4.84 (2H, s), 6.22 (1H, s), 6.62 (1H, s), 7.13 (1H, dd, J=7.5, 1Hz), 7.28-7.41 (6H, m)
MASS (m/z) : 548 (M^++1)

33) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,2-dimethylpropyl)urea
mp : 175-178°C
NMR ($CDCl_3$, δ) : 0.89 (9H, s), 2.35 (3H, s), 2.45 (3H, s), 2.47 (3H, s), 2.48 (3H, s), 3.18 (2H, s), 4.83 (2H, s), 6.15 (1H, s), 6.62 (1H, s), 7.15 (1H, dd, J=7.5, 1Hz), 7.29 (1H, s), 7.39-7.48 (5H, m)
MASS (m/z) : 568 (M^++1)

34) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-bromophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-

butylurea
mp : 185.5-187°C
NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.24 (2H, sextet, J=7Hz), 1.46-1.53 (2H, m), 2.40 (3H, s), 2.44 (3H, s), 2.50 (3H, s), 2.51 (3H, s), 3.30 (2H, t, J=7Hz), 4.80 (2H, s), 6.03 (1H, s), 6.66 (1H, s), 7.17 (1H, dd, J=8, 1Hz), 7.31-7.43 (2H, m), 7.51 (4H, AB, J=8, 8Hz)
MASS (m/z) : 600 (M^++2), 598 (M^+)

35) N-Benzyl-N'-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-N-[3-(4-bromophenyl)-5-methylbenzofuran-2-ylmethyl]urea
mp : 157.5-158.5°C
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.44 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 4.50 (2H, s), 4.72 (2H, s), 6.29 (1H, s), 6.67 (1H, s), 7.06-7.10 (2H, m), 7.17 (1H, dd, J=8, 1Hz), 7.21-7.31 (6H, m), 7.42 (1H, d, J=8Hz), 7.59 (2H, d, J=8Hz)
MASS (m/z) : 634 (M^++2), 632 (M^+)

Example 7

The following compounds were obtained according to a similar manner to that of Example 5 except that the corresponding benzofuranylmethylamine derivatives were prepared by treating the corresponding hydrochloride thereof with 1N aqueous sodium hydroxide.

1) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-cyclopropylmethylurea
mp : 195-196°C
NMR ($CDCl_3$, δ) : 0.05 (2H, q, J=7.5Hz), 0.44 (2H, q, J=7.5Hz), 0.90-1.00 (1H, m), 2.39 (3H, s), 2.43 (3H, s), 2.48 (3H, s), 2.50 (3H, s), 3.22 (2H,

d, J=7.5Hz), 4.93 (2H, s), 6.20 (1H, s), 6.67 (1H, s), 7.16 (1H, d, J=8Hz), 7.31 (1H, s), 7.39-7.47 (5H, m)

MASS (m/z) : 552 (M^++1)

2) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-cyclopropylmethyl-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea

mp : 178-180°C

NMR ($CDCl_3$, δ) : 0.02 (2H, q, J=7.5Hz), 0.37 (2H, q, J=7.5Hz), 0.86-0.98 (1H, m), 2.40 (3H, s), 2.42 (3H, s), 2.43 (3H, s), 2.50 (3H, s), 2.52 (3H, s), 3.20 (2H, d, J=7Hz), 4.92 (2H, s), 6.30 (1H, s), 6.67 (1H, s), 7.14 (1H, d, J=7.5Hz), 7.29-7.42 (6H, m)

MASS (m/z) : 532 (M^++1)

3) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(E)-2-butenyl]-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]urea

mp : 169-172°C

NMR ($CDCl_3$, δ) : 1.60 (3H, d, J=6Hz), 2.40 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.51 (3H, s), 3.87 (2H, d, J=6Hz), 4.80 (2H, s), 5.36-5.46 (2H, m), 6.17 (1H, s), 6.66 (1H, s), 7.16 (1H, dd, J=8, 1Hz), 7.33 (1H, s), 7.41 (1H, d, J=8Hz), 7.48 (4H, s)

MASS (m/z) : 552 (M^++1)

4) N-[2,4-Bis(methylthio)-6-methylpyridin-3-yl]-N'-[(E)-2-butenyl]-N'-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]urea

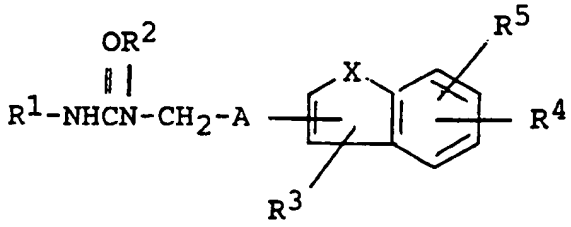
mp : 155-157°C

NMR ($CDCl_3$, δ) : 1.57 (3H, d, J=6Hz), 2.40 (3H, s), 2.42 (3H, s), 2.43 (3H, s), 2.49 (3H, s), 2.50

(3H, s), 3.82 (2H, d, J=6Hz), 4.80 (2H, s),
5.33-5.39 (2H, m), 6.25 (1H, s), 6.64 (1H, s),
7.13 (1H, dd, J=7.5, 1Hz), 7.29-7.42 (6H, m)
MASS (m/z) : 532 (M^++1)

C L A I M S

1. A compound of the formula :



(I)

wherein R^1 is a heterocyclic group which may be substituted with substituent(s) selected from the group consisting of lower alkyl, lower alkylthio, halogen, nitro, amino, lower alkylamino, lower alkoxy and acylamino,

R^2 is hydrogen; alkyl; lower alkenyl; cycloalkyl; or lower alkyl which is substituted with halogen, lower alkoxy, lower alkylthio, cyclo(lower)alkyl, cyclo(lower)alkenyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy, lower alkoxy, ar(lower)alkoxy and lower alkylamino;

R^3 is hydrogen, lower alkyl or aryl which may be substituted with halogen, nitro, amino or lower alkylamino,

R^4 is hydrogen, halogen, lower alkyl, lower alkoxy or aryl which may be substituted with halogen,

R^5 is hydrogen, halogen, lower alkyl or aryl,

A is a single bond or lower alkylene, and

X is O, S or NH,

provided that at least one of unsubstituted or substituted aryl for R^3, R^4 and R^5 is aryl except phenyl or substituted aryl,

and pharmaceutically acceptable salts thereof.

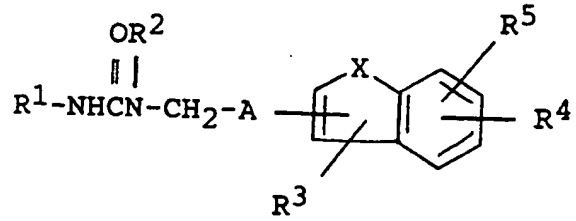
2. A compound according to claim 1,
wherein R^1 is pyridyl or quinolyl, each of which may be substituted with substituent(s) selected from the group consisting of lower alkyl and lower alkylthio,
R^2 is alkyl, cycloalkyl, or lower alkyl substituted with cyclo(lower)alkyl, furyl, thienyl or aryl optionally substituted with halogen, hydroxy, lower alkoxy, ar(lower)alkoxy or lower alkylamino,
R^3 is phenyl substituted with lower alkyl or halogen,
R^4 is lower alkyl or halogen,
R^5 is hydrogen,
A is a single bond, and
X is O.

3. A compound according to claim 2,
wherein R^1 is pyridyl or quinolyl, each of which is substituted with substituent(s) selected from the group consisting of lower alkyl and lower alkylthio, and
R^2 is cyclo(lower)alkyl or lower alkyl optionally substituted with cyclo(lower)alkyl, furyl or phenyl optionally substituted with lower alkyl.

4. A compound according to claim 3,

wherein R^2 is lower alkyl optionally substituted with furyl or phenyl, and
R^4 is lower alkyl.

5. A process for preparing a compound of the formula :



(I)

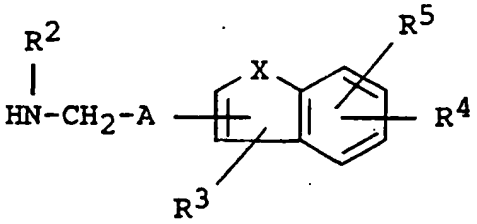
wherein R^1 is a heterocyclic group which may be substituted with substituent(s) selected from the group consisting of lower alkyl, lower alkylthio, halogen, nitro, amino, lower alkylamino, lower alkoxy and acylamino,
R^2 is hydrogen; alkyl; lower alkenyl; cycloalkyl; or lower alkyl which is substituted with halogen, lower alkoxy, lower alkylthio, cyclo(lower)alkyl, cyclo(lower)alkenyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy, lower alkoxy, ar(lower)alkoxy and lower alkylamino;
R^3 is hydrogen, lower alkyl or aryl which may be substituted with halogen, nitro, amino or lower alkylamino,
R^4 is hydrogen, halogen, lower alkyl, lower alkoxy or aryl which may be substituted with halogen,
R^5 is hydrogen, halogen, lower alkyl or aryl,

A is a single bond or lower alkylene, and
X is O, S or NH,
provided that at least one of unsubstituted or substituted aryl for R^3, R^4 and R^5 is aryl except phenyl or substituted aryl,
or pharmaceutically acceptable salts thereof, which comprises,

(a) reacting a compound of the formula :

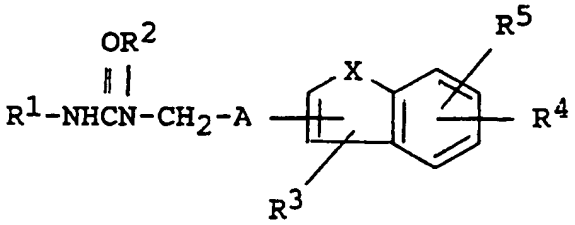
$$R^1\text{-}NCO \qquad (II)$$

with a compound of the formula :



(III)

or its salt to provide a compound of the formula :



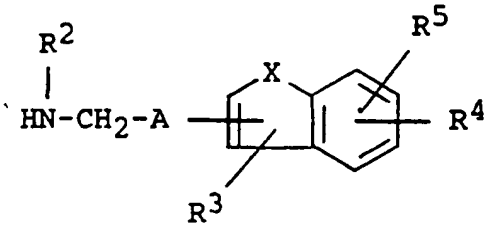
(I)

or its salt, in the above formulas,
R^1, R^2, R^3, R^4, R^5, A and X are each as defined above, or

(b) subjecting a compound of the formula :

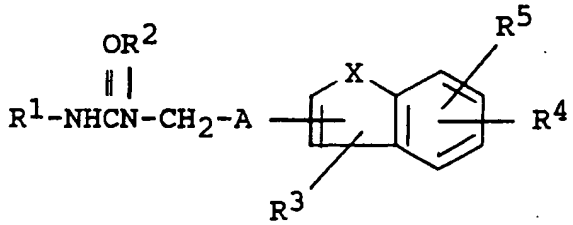
$$R^1\text{-}NH_2 \qquad (IV)$$

or its salt and a compound of the formula :



(III)

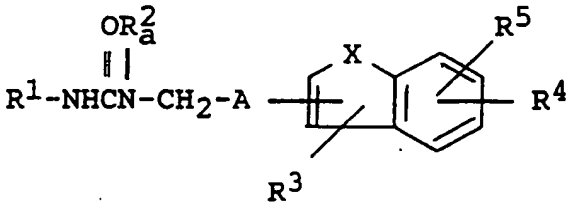
or its salt to formation reaction of ureido group to provide a compound of the formula :



(I)

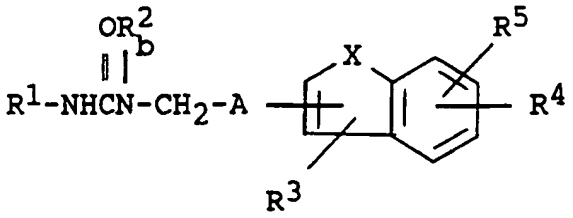
or its salt, in the above formulas, R^1, R^2, R^3, R^4, R^5, A and X are each as defined above, or

(c) subjecting a compound of the formula :



(Ia)

or its salt to dealkylation reaction to provide a compound of the formula :



(Ib)

or its salt, in the above formulas,
R^1, R^3, R^4, R^5, A and X are each as defined above,
R^2_a is lower alkyl which is substituted with aryl substituted with lower alkoxy, and
R^2_b is lower alkyl which is substituted with aryl substituted with hydroxy.

6. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

7. A compound of claim 1 for use as a medicament.

8. A method of therapeutic treatment and/or prevention of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby which comprises administering an effective amount of a compound of claim 1 to human beings or animals.

9. Use of a compound of claim 1 for the manufacture of a medicament for treating and/or preventing hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby in human beings or animals.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 94/00785

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D405/12 C07D405/14 C07D409/14 A61K31/44 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 506 532 (LIPHA, LYONNAISE INDUSTRIELLE PHARMACEUTIQUE) 30 September 1992 see abstract; claims 1-3; example 40 see page 3, line 24 - line 26 see page 4, line 8 - line 18 ---	1-4,6-9
X	EP,A,0 527 687 (ADIR ET COMPAGNIE) 17 February 1993 see claim 1 ---	1-4,6,7
A	EP,A,0 512 570 (FUJISAWA PHARMACEUTICAL CO., LTD.) 11 November 1992 cited in the application see the whole document --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 1994	18. 08. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 94/00785

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,93 24458 (PFIZER INC.) 9 December 1993 cited in the application see abstract; claims	1-4,6-9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 94/ 00785

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International application No.
PCT/JP 94/00785

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0506532	30-09-92	FR-A-	2674522	02-10-92
		AU-A-	1309492	01-10-92
		JP-A-	5097802	20-04-93
		OA-A-	9573	31-01-93
		US-A-	5219859	15-06-93
EP-A-0527687	17-02-93	FR-A-	2680366	19-02-93
		AU-B-	649864	02-06-94
		AU-A-	2095092	18-02-93
		CA-A-	2075876	14-02-93
		US-A-	5308866	03-05-94
		US-A-	5276051	04-01-94
EP-A-0512570	11-11-92	AU-A-	1528292	12-11-92
		CN-A-	1067886	13-01-93
		JP-A-	5140102	08-06-93
WO-A-9324458	09-12-93	AU-B-	4028393	30-12-93
		HU-A-	64303	28-12-93